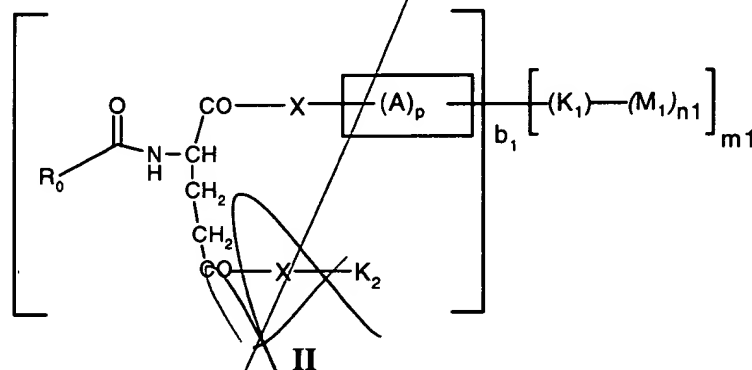


## CLAIMS:

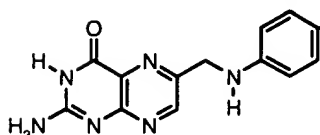
1. A diagnostic, therapeutic or radiotherapeutic or chemotherapeutic composition for visualization, therapy, chemotherapy or radiotherapy of tissues or organs that overexpress folate-binding protein comprising:

- a) a folate-receptor binding ligand comprising one or more folate-receptor binding residues, at least one of which is conjugated through its alpha carboxylate via an optional linking group to one or more macrocyclic or non-macrocyclic metal-chelating ligand radicals that are optionally chelated to paramagnetic, superparamagnetic, radioactive or non-radioactive metals capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic, chemotherapeutic, or radiotherapeutic effect; and
- b) a pharmaceutically acceptable carrier.

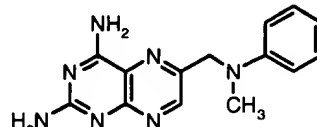
2. The diagnostic, therapeutic or radiotherapeutic composition of claim 1 wherein said folate receptor binding ligand has the structure of formula II:



wherein  $R_0$  is a folate-receptor binding residue of formula:



or



each X is independently -O-, -S-, -NH-, or -NR<sub>1</sub>-;

n<sub>1</sub> is 0 or 1;

b<sub>1</sub> is 1 to 3;

m<sub>1</sub> is 1 to 81;

each K<sub>1</sub> is independently

- a) a macrocyclic or non-macrocyclic metal-chelating ligand radical that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal M<sub>1</sub>,

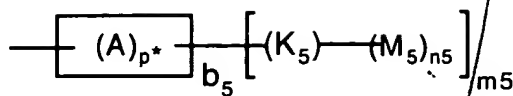
or

- b) a chemotherapeutic drug;

-K<sub>2</sub> is -H-, -alkyl-, -alkenyl-, -alkynyl-, -alkoxy-, -aryl-, -alkyl,

-CON(R<sub>2</sub>)<sub>2</sub>-, -glutamate-, -polyglutamate-, or -K<sub>3</sub>;

-K<sub>3</sub> is



wherein

-K<sub>5</sub> is either

- a) a macrocyclic or non-macrocyclic metal-chelating ligand that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal M<sub>5</sub>, or  
b) a chemotherapeutic drug

n<sub>5</sub> is 0 or 1;

b<sub>5</sub> is 1 to 3;

m<sub>5</sub> is 1 to 81;

-(A)<sub>p</sub>- and -(A)<sub>p</sub>\*- are each independently optional linkers comprising a straight or branched chain wherein the moieties "A" are the same or different and selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sub>3</sub>-, -CR<sub>4</sub>R<sub>5</sub>-, -CH=CH-, -CH=CR<sub>6</sub>-, >CR<sub>7</sub>-CR<sub>8</sub>-, -C=C-, -CR<sub>9</sub>=CR<sub>10</sub>-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -HC=N-, -CR<sub>11</sub>=N-, -NR<sub>12</sub>-, -

CS-,  $\text{---} \overset{\text{H}}{\underset{|}{\text{C}}} \text{---}$ ,  $\text{---} \overset{\text{H}}{\underset{|}{\text{C}}} \text{---}$ ,  $\text{---} \overset{\text{H}}{\underset{|}{\text{N}}} \text{---}$ , and

p and p\* are independently 0 to 24,

or -X-[(A)<sub>p</sub>]p- and -X-[(A)<sub>p</sub>\*]p\*- may each independently be the group -Q-

wherein -Q- is -[C(R')(R'')]s<sub>1</sub>-[C(t)(R<sub>21</sub>)]s<sub>2</sub>--[C(R<sub>22</sub>)(R<sub>23</sub>)]s<sub>3</sub>-X<sub>3</sub>-Y-

X<sub>4</sub>-;

wherein

each s<sub>1</sub>, s<sub>2</sub>, s<sub>3</sub>, and s<sub>4</sub> is independently 0 to 2;

each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> is independently a single bond, -O-, -S-, or -N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or Y<sub>1</sub> wherein,

Y<sub>1</sub> is -C(=X<sub>5</sub>)-X<sub>6</sub>-W-, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>))OH, -P(O)(OR<sub>30</sub>))OR<sub>31</sub>, -P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub>, -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or C(O)NH(R<sub>37</sub>);

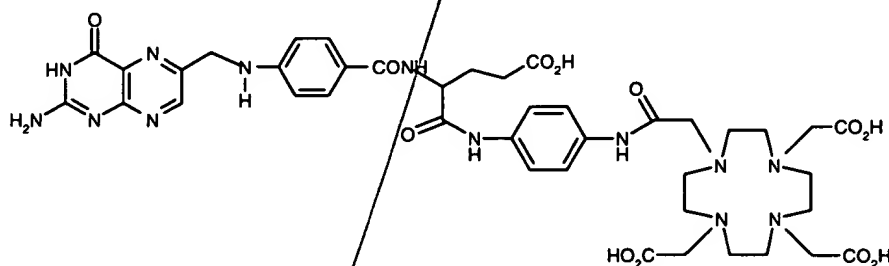
each R' and R'' is independently a single bond, H, alkyl, alkoxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

each R<sub>3</sub> through R<sub>5</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>21</sub> through R<sub>23</sub>, and R<sub>25</sub> through R<sub>27</sub> is independently H, alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

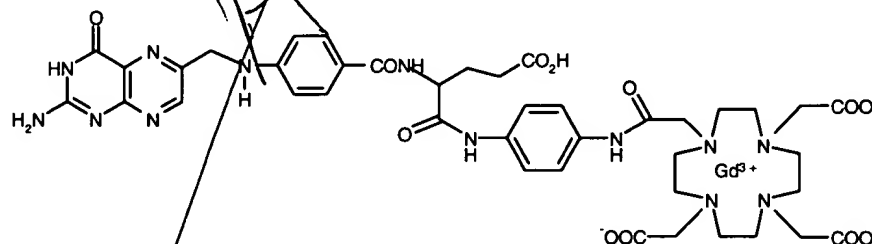
each R<sub>1</sub>, R<sub>2</sub>, R<sub>6</sub>, R<sub>9</sub> through R<sub>12</sub>, R<sub>24</sub>, and R<sub>28</sub> through R<sub>37</sub> is independently H, alkyl,

alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle;  
or a pharmaceutically acceptable salt thereof.

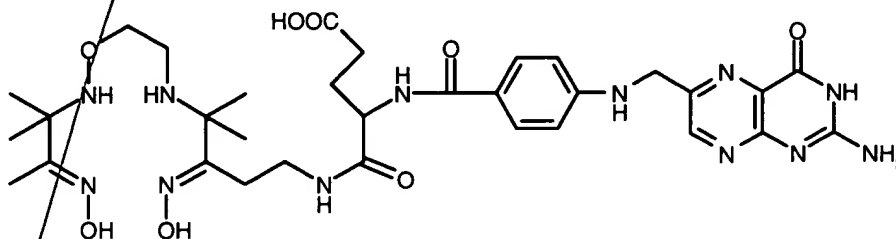
- 5 3. The composition of claim 2 for use in nuclear medicine or magnetic resonance imaging applications wherein  $K_1$  of the compounds of formula II is a macrocyclic or non-macrocyclic metal-chelating ligand that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal  $M_1$ , and  $K_2$  is other than  $K_3$ .
- 10 4. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand has the structure:



- 15 5. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand has the structure:

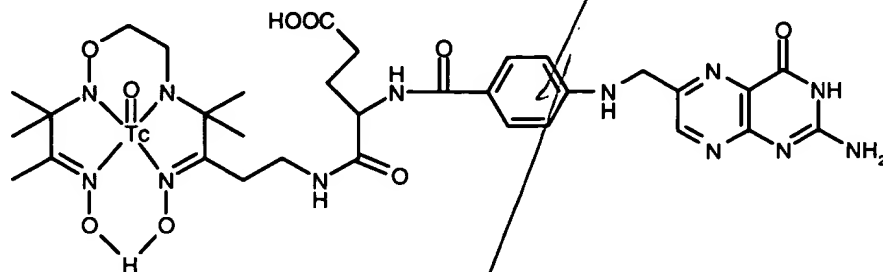


- 20 6. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand, 12-N-(N-Pteroyl-( $\alpha$ )-L-glutamyl)-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime has the structure:

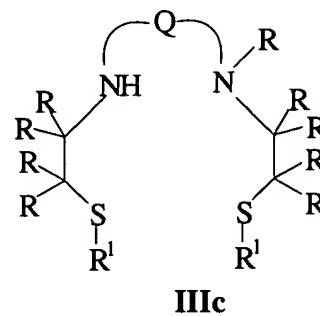
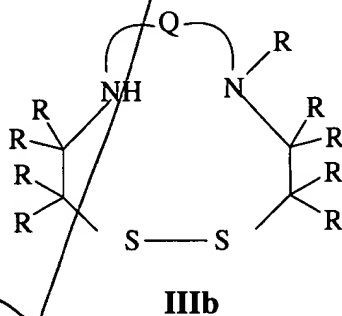
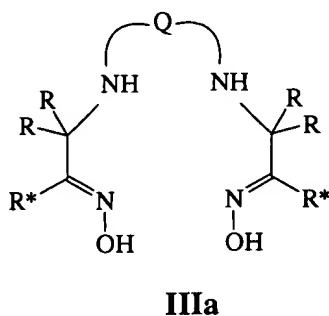


7. The diagnostic, therapeutic, or radiotherapeutic composition of claim 2 wherein said folate-receptor binding ligand, Technetium oxo-12-N-(N-Pteroyl-( $\alpha$ )-L-glutamyl)-3,3,9,9-

tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime has the structure:



8. The composition of claim 2 wherein  
 b1 = 1 to 3;  
 m1 = 1;  
 K<sub>2</sub> is other than K<sub>3</sub>; and  
 K<sub>1</sub> is a metal chelating ligand radical of formula IIIa - IIIc:



wherein

Q is the group  $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$ ,  
 wherein

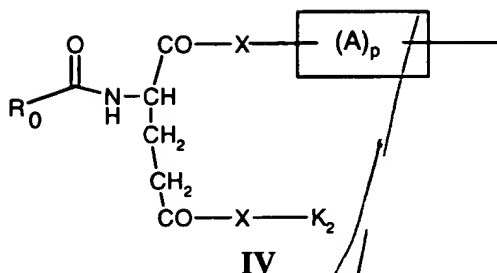
$Y^1$  and  $Y^2$  are independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n is 0 or 1; and m1, m2 and m3 are integers independently selected from 0 to 4,  
 provided that the sum of m1 and m2 is greater than zero;

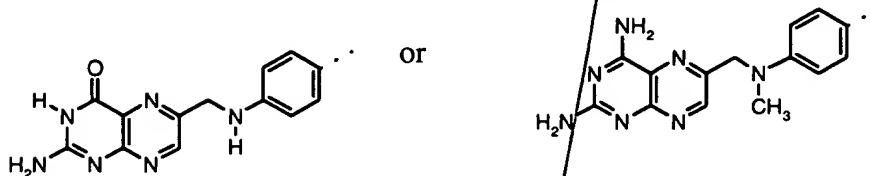
all R and R\* groups are independently  $-R^2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OR^2$ ,  $-COOR^2$ ,  $-CON(R^2)_2$ ,  $-N(R^2)_2$ ,  $-alkyl-COOR^2$ ,  $-alkyl-C(O)-N(R^2)_2$ ;  $-alkyl-N(R^2)_2$ ;  $-C(O)-OR^2$ ;  $-C(O)-N(R^2)_2$ ;  $-aryl-N(R^2)_2$ ; acyl; acyloxy; heterocyclo; hydroxyalkyl;  $-SO_2-R^2$ ;  $-alkyl-SO_2-R^2$ ; or  $-R^3$ , wherein  $-R^3$  is a folate-receptor binding residue of formula IV; or

two R groups, or an R group and an R\* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R\* groups above,

with the proviso that a carbon atom bearing an R group is not directly bonded to more than one heteroatom; and that one to three of R or R\* is, or contains a folate-receptor binding radical  $-R^3$  of formula IV:



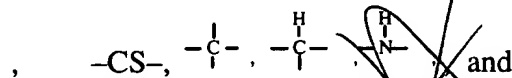
wherein  $R_0$  is a folate-receptor binding residue of formula:



each X is independently -O-, -S-, -NH- or -N( $R_2$ )-;

$K_2$  is -H-, -alkyl-, -alkenyl-, -alkynyl-, -alkoxy-, -aryl-, -alkyl-, -CON( $R_2$ )<sub>2</sub>-, -glutamate-, or -polyglutamate-;

-(A)<sub>p</sub>- is an optional linker comprising a straight or branched chain wherein the moieties "A" are the same or different and selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sub>3</sub>-, -CR<sub>4</sub>R<sub>5</sub>-, -CH=CH-, -CH=CR<sub>6</sub>-, >CR<sub>7</sub>-CR<sub>8</sub><-, >C=C<-, -CR<sub>9</sub>=CR<sub>10</sub>-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -HC=N-, -CR<sub>11</sub>=N-, -NR<sub>12</sub>-



p and p\* are independently 0 to 24,

$R^1$  is hydrogen, a thiol protecting group, or the group - $R^3$  defined above;

$R_2$  is independently hydrogen, alkyl, cycloalkyl, hydroxyalkyl, aryl, or arylalkyl;

$R_3$  through  $R_8$  are independently hydrogen, alkyl, alkoxy, hydroxy, or aryl;

$R^2$  and  $R_9$  through  $R_{12}$  are independently hydrogen, alkyl, or aryl;

or a pharmaceutically acceptable salt thereof.

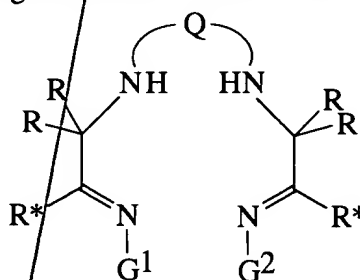
9. The composition of claim 2 wherein

b1 = 1 to 3;

m1 = 1;

$K_2$  is other than  $K_3$ ; and

$K_1$  is a metal chelating ligand radical of formula V:



## V

wherein

Q is the group  $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$ ;

$Y^1$  and  $Y^2$  are each independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that  $m1 + m2 + n + n1$  is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

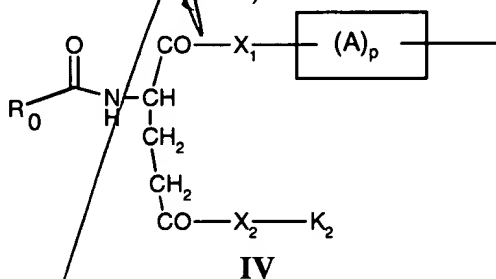
each R and R\* group is independently:  $R^1$ , -alkoxy, -hydroxy, -halogen, especially fluoro, -haloalkyl,  $-OR^1$ ,  $-C(O)-R^1$ ,  $-C(O)-N(R^1)_2$ ,  $-N(R^1)_2$ ,  $-N(R^1)-COR^1$ , -alkyl- $C(O)-OR^1$ , -alkyl- $C(O)-N(R^1)_2$ , -alkyl- $N(R^1)_2$ , -alkyl- $N(R^1)-COR^1$ , -aryl- $C(O)-OR^1$ , -aryl- $C(O)-N(R^1)_2$ , aryl- $N(R^1)_2$ , -aryl- $N(R^1)-COR^1$ , -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, alkoxyalkyl, hydroxyaryl, arylalkyl,  $-SO_2-R^1$ , -alkyl- $SO_2-R^1$ , or  $-R^3$ , wherein  $-R^3$  is a folate-receptor binding residue of formula IV; or

two R groups, or an R group and an R\* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R\* groups above;

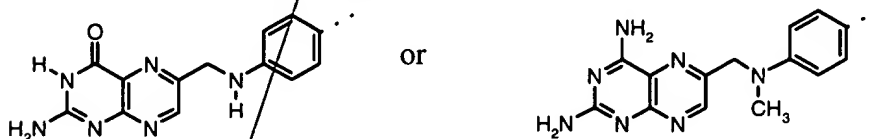
each  $R^1$  is independently hydrogen, alkyl, alkenyl, alkynyl or aryl; and

each  $G^1$  and  $G^2$  is each independently  $-OH$  or  $-(NR^2)_2$ ;

with the proviso that at least one of  $G^1$  or  $G^2$  is  $-(NR^2)_2$ , where each  $R^2$  is independently hydrogen, alkyl, aryl, acyl or  $-R^1$  and one to three of R, R\*, or  $R^2$  is, or contains a folate-receptor binding radical  $-R^3$  of formula IV:



wherein  $R_0$  is a folate-receptor binding residue of formula:



each X is independently  $-O-$ ,  $-S-$ ,  $-NH-$  or  $-N(R_2)-$ ;

$K_2$  is  $-H$ , -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl,  $-CON(R_2)_2$ , -glutamate, or -polyglutamate; wherein  $R_2$  is independently hydrogen, alkyl, or aryl;

A is a linking group as defined in claim 1; and p is 0 to 24;

or a salt thereof.

10. The composition of claim 2 wherein

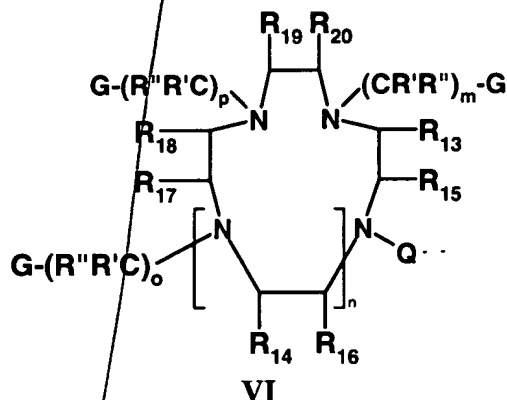
$b_1$  is 1;

$m_1 = 1$ ;

$-K_2$  is other than  $-K_3$ ;

5  $-X-[(A)p]-$  is, in its entirety, the group  $-Q-$  as defined below;

$-K_1$  is a macrocyclic ligand radical of formula VI:



wherein

$n$  is 0 or 1;

10 each  $m$ ,  $o$ , and  $p$  is independently 1 or 2;

$-Q-$  is  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$ ; wherein

$s1$ ,  $s2$ ,  $s3$ , and  $s4$  are independently 0 to 2;

$X3$ ,  $X4$ ,  $X5$ , and  $X6$  are independently a single bond,  $-O-$ ,  $-S-$ , or  $-N(R_{24})-$ ;

15  $Y$  is a single bond,  $-C(R_{25})(R_{26})-$ , or  $Y1$ ,

wherein

$Y1$  is  $-C(=X5)-X6-W-$ , wherein

$W$  is a single bond,  $-alkylidene-$ ,  $-cycloalkylidene-$ ,  $-arylidene-$ ,  $-alkenylidene-$ , or  $-alkynylidene-$ , whose carbon atoms may or may not be substituted;

20  $t$  is  $H$ ,  $R_{27}$ ,  $-C(O)OR_{28}$ ,  $-P(O)(OR_{29})OH$ ,  $-P(O)(OR_{30})OR_{31}$ ,

$-P(O)(OR_{32})R_{33}$ ,  $-P(O)(OH)R_{34}$ ,  $-C(O)N(R_{35})(R_{36})$ , or  $C(O)NH(R_{37})$ ;

each  $G$  is independently  $-C(O)OR''$ ,  $-P(O)(OR''')OH$ ,  $-P(O)(OR''')_2$ ,

$-P(O)(OR''')R''$ ,  $-P(O)(OH)R''$ ,  $C(O)N(R''')_2$ , or  $C(O)NH(R''')$ ;

25 each  $R'$  and  $R''$  is independently a single bond,  $H$ , alkyl, alkoxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

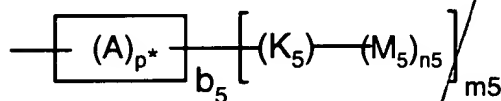
each  $R'''$  is independently a  $H$ , alkyl, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

30 each  $R_{13}$  through  $R_{23}$ , and  $R_{25}$  through  $R_{27}$  is independently  $H$ , alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

each  $R_{24}$ , and  $R_{28}$  through  $R_{37}$  is independently  $H$ , alkyl, alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

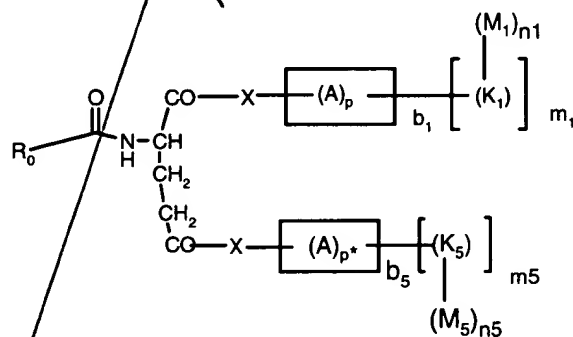
or R<sub>13</sub> together with R<sub>15</sub>, and R<sub>17</sub> together with R<sub>18</sub>, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R<sub>13</sub> and R<sub>15</sub> are each hydrogen and R<sub>17</sub>, together with R<sub>18</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R<sub>13</sub>, together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen;

11. The composition of claim 2 wherein -K<sub>2</sub> is



and both -K<sub>1</sub> and -K<sub>5</sub> are macrocyclic or non-macrocyclic metal chelates that are each optionally chelated to radioactive, nonradioactive, paramagnetic or superparamagnetic metals M<sub>1</sub> or M<sub>5</sub>.

12. The composition of claim 11 for use in nuclear medicine or magnetic resonance imaging applications comprising a folate-receptor binding ligand of formula IIa:



IIa

wherein

b<sub>1</sub> and b<sub>5</sub> = 1;

m<sub>1</sub> and m<sub>5</sub> = 1;

M<sub>1</sub> and M<sub>5</sub> are independently paramagnetic, superparamagnetic or radioactive metals;

n<sub>1</sub> and n<sub>2</sub> are independently = 0 or 1;

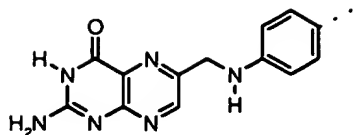
X is -O-, -S-, or -NR<sup>2</sup>-;

-R<sup>2</sup> is -hydrogen, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -arylalkyl;

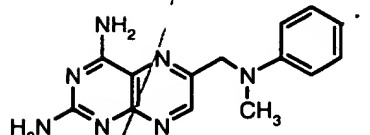
-[(A)<sub>p</sub>]- and -[(A)<sub>p</sub>\*]- are optional linking groups;

R<sub>0</sub> is a folate-receptor binding residue of formula:



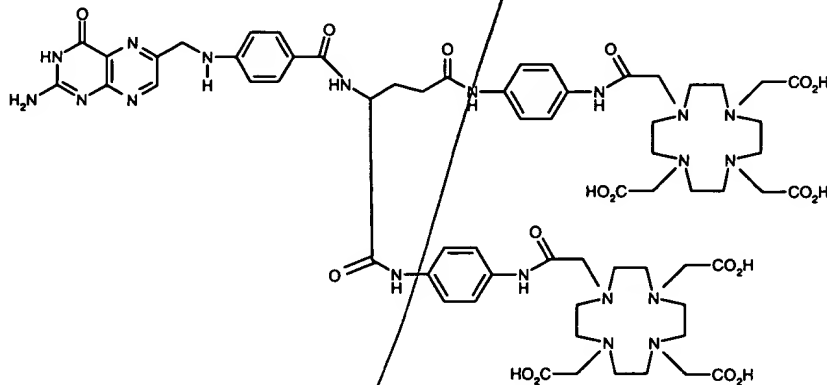


OR

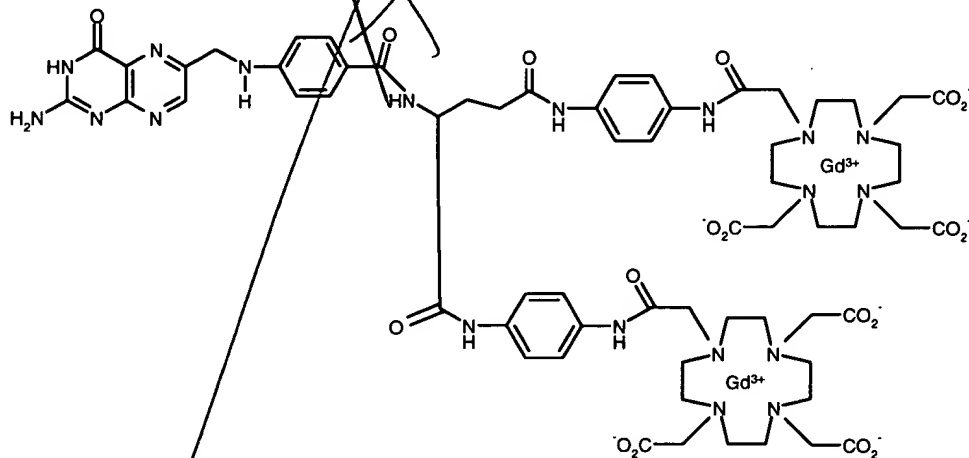


and  $K_1$  and  $K_5$  are metal chelating ligand radicals.

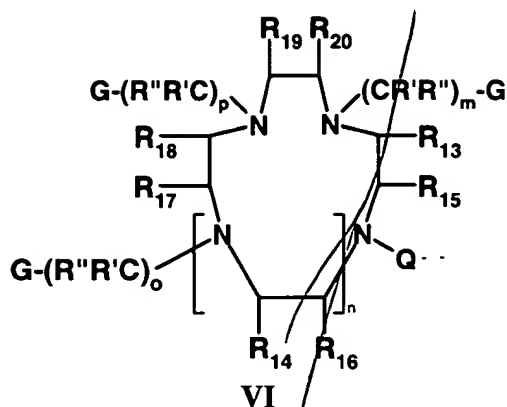
13. The composition of claim 11 wherein said folate receptor binding ligand has the structure:



14. The composition of claim 11 comprising the folate receptor binding ligand Bis (Gd-DO3A-APA)-folate having the structure:



15. The composition of claim 11 wherein both  $-X-[(A)p]-K_1$  and  $-X-[(A)p^*]-K_5$  are each in their entirety, macrocyclic ligand radicals of formula VI:



wherein

**n** is 0 or 1;

each  $m$ ,  $o$ , and  $p$  is independently 1 or 2;

Q is  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$ ;

wherein

$s_1, s_2, s_3$ , and  $s_4$  are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or Y<sub>1</sub>;

wherein

Y1 is  $-C(=X5)-X6-W-$ , wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is -H, -R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>)OH, -P(O)(OR<sub>30</sub>)OR<sub>31</sub>,

-P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub>, -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or C(O)NH(R<sub>37</sub>);

each G is independently -C(O)OR<sup>'''</sup>, -P(O)(OR<sup>'''</sup>)OH, -P(O)(OR<sup>'''</sup>)<sub>2</sub>, -P(O)(OR<sup>'''</sup>)R<sup>'''</sup>, -P(O)(OH)R<sup>'''</sup>, C(O)N(R<sup>'''</sup>)<sub>2</sub>, or C(O)NH(R<sup>'''</sup>);

each R' and R'' is independently a single bond, H, alkyl, alkoxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

each R''' is independently a H, alkyl, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted,

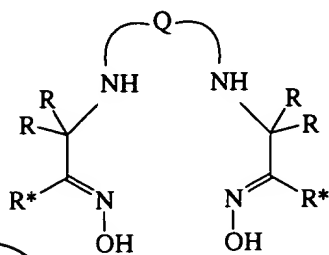
each R<sub>13</sub> through R<sub>23</sub>, and R<sub>25</sub> through R<sub>27</sub> is independently H, alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

each R<sub>24</sub>, and R<sub>28</sub> through R<sub>37</sub> is independently H, alkyl, alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

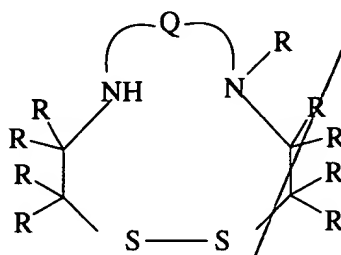
or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R13 and R15 are each hydrogen and R17, together with R18, forms a fused fully or partially saturated non-aromatic

cyclohexyl ring as defined above, or R<sub>13</sub>, together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen;  
or a pharmaceutically acceptable salt thereof.

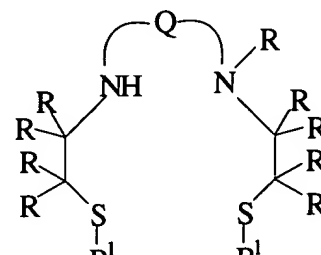
16. The compositions of claim 11 wherein -[(A)p]-K<sub>1</sub> and -[(A)p\*]-K<sub>5</sub> are each in their entirety, polydentate ligands radicals of formula IIIa - IIIc:



IIIa



IIIb



IIIc

wherein

Q is the group  $-(C(RR))_{m1}-Y^1(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$ ,

wherein

$Y^1$  and  $Y^2$  are independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n is 0 or 1; and m<sub>1</sub>, m<sub>2</sub> and m<sub>3</sub> are integers independently selected from 0 to 4, provided that the sum of m<sub>1</sub> and m<sub>2</sub> is greater than zero;

all R and R\* groups are independently  $-R^4$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OR^5$ ,  $-COOR^5$ ,  $-CON(R^5)_2$ ,  $-N(R^5)_2$ ,  $-alkyl-COOR^5$ ,  $-alkyl-C(O)-N(R^5)_2$ ,  $-alkyl-N(R^5)_2$ ,  $-C(O)OR^5$ ,  $-C(O)N(R^5)_2$ ,  $-aryl-N(R^5)_2$ ,  $-acyl$ ,  $-acyloxy$ ,  $-heterocyclo$ ,  $-hydroxyalkyl$ ,  $-SO_2-R^5$ ,  $-alkyl-SO_2-R^5$ ; or  $-R^3$ ;

wherein

each  $-[R^3]-$  is, in its entirety, the linking group  $-[(A)p]-$  or  $-[(A)p*]-$  that serves to couple the metal chelating ligand radical to  $-X-$ ;

each  $-R^4$  is independently  $-H$ ,  $-alkyl$ ,  $-alkoxy$ ,  $-hydroxy$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted;

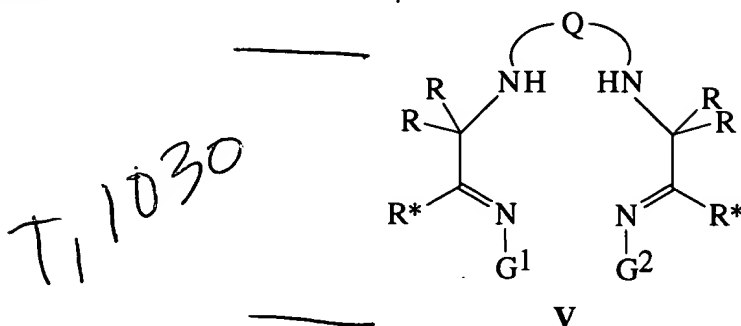
each  $-R^5$  is independently  $-H$ ,  $-alkyl$ ,  $-aryl$ ,  $-cycloalkyl$  or  $-hydroxyalkyl$ , each of which is independently substituted;

with the provisos that a carbon atom bearing an R group is not directly bonded to more than one heteroatom; and

at least one R or R\* group on each  $-K_1$  and  $-K_5$  is  $-[R^3]-$ ;

or a pharmaceutically acceptable salt thereof.

A *2/11* The composition of claim 11 wherein both  $-K_1$  and  $-K_5$  are metal-chelating ligand radicals of formula V:



wherein

$-Q-$  is the group  $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2)-(C(RR))_{m3}n1$ ;

$Y^1$  and  $Y^2$  are each independently  $-CH_2-$ ,  $-NR^5-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

$n$  and  $n1$  are each independently 0 or 1; and  $m1$ ,  $m2$  and  $m3$  are independently 0 or an integer from 1 to 4; provided that  $m1$  and  $m2$  are not both 0, that  $m1 + m2 + n + n1$  is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each  $-R$  and  $-R^*$  group is independently:  $-R^4$ ; -alkoxy; -hydroxy; -halogen, especially fluoro; -haloalkyl;  $-OR^5$ ;  $-C(O)-R^5$ ,  $-C(O)-N(R^5)_2$ ,  $-N(R^5)_2$ ,  $-N(R^5)-COR^5$ ; -alkyl- $C(O)-OR^5$ , -alkyl- $C(O)-N(R^5)_2$ , -alkyl- $N(R^5)_2$ , -alkyl- $N(R^5)-COR^5$ , -aryl- $C(O)-OR^5$ , -aryl- $C(O)-N(R^5)_2$ , aryl- $N(R^5)_2$ , -aryl- $N(R^5)-COR^5$ , -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, alkoxyalkyl, hydroxyaryl, arylalkyl,  $-SO_2-R^5$ , -alkyl- $-SO_2-R^5$ , or  $-[R^3]-$

wherein

each  $-[R^3]-$  is, in its entirety, the linking group  $-[(A)p]-$  or  $-[(A)p^*]-$  that serves to couple the metal chelating ligand radical  $-K_1$  or  $-K_5$  to  $-X-$ ;

each  $-R^4$  is independently  $-H$ , -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each  $-R^5$  is independently  $-H$ , -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is optionally substituted;

or

two R groups, or an R group and an  $R^*$  group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or  $R^*$  groups above;

each  $G^1$  and  $G^2$  is independently  $-OH$  or  $-(NR^6)_2$ ; with the proviso that at least one of  $G^1$  or  $G^2$  is  $-(NR^6)_2$ , where each  $R^6$  is independently hydrogen, alkyl, aryl, acyl or  $-[R^3]-$ ; and

A is a linking group; and p is 0 or a positive integer;

with the proviso that at least one R,  $R^*$ , or  $R^6$  group is  $-[R^3]-$ ;

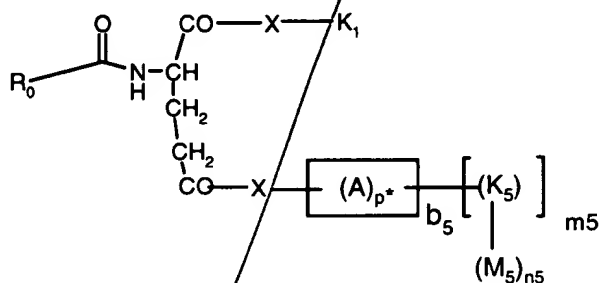
or a pharmaceutically acceptable salt thereof.

18. A diagnostic, therapeutic or radiotherapeutic composition for visualization, therapy or radiotherapy of tissues or organs that overexpress folate-binding protein using nuclear medicine, magnetic resonance imaging or neutron capture radiotherapy applications comprising:

5

- a) a folate-receptor binding ligand and
- b) a pharmaceutically acceptable carrier

wherein said folate-receptor binding ligand has the structure of formula IIb:



IIb

10

wherein

-K<sub>1</sub> is -H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R<sub>2</sub>)<sub>2</sub>, -glutamate, or -polyglutamate;

-K<sub>5</sub> is a polydentate metal chelating ligand;

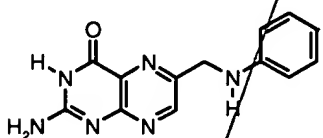
M<sub>5</sub> is a radioactive, paramagnetic or superparamagnetic metal;

15

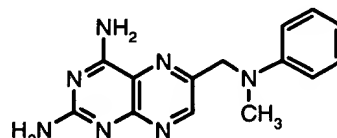
each -X- is independently -O-, -S-, -NH-, or -NR<sub>1</sub>-;

b<sub>5</sub> = 1 to 3, m<sub>5</sub> = 1; n<sub>5</sub> is 0 or 1;

-R<sub>0</sub> is a folate-receptor binding residue of formula:



or



20

each -[(A)<sub>p\*</sub>]- is an optional linker independently comprising a straight or branched chain made up of "p\*" individual (A) moieties that are the same or different and are selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sub>3</sub>-, -CR<sub>4</sub>R<sub>5</sub>-, -CH=CH-, -CH=CR<sub>6</sub>-, >CR<sub>7</sub>-CR<sub>8</sub><-, >C=C<-, -CR<sub>9</sub>=CR<sub>10</sub>-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -

25

HC=N-, -CR<sub>11</sub>=N-, -NR<sub>12</sub>-, -CS-, and  $\begin{matrix} | \\ -C- \\ | \end{matrix}$ ,  $\begin{matrix} H \\ | \\ -C- \\ | \end{matrix}$ ,  $\begin{matrix} H \\ | \\ -N- \\ | \end{matrix}$ ;

and p\* is 0 to 24;

or -X-[(A)<sub>p\*</sub>]- is, in its entirety, the group -Q-

wherein

-Q- is  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$ ;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or -Y1-

wherein,

Y1 is  $-C(=X5)-X6-W-$ , wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-,  
or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>))OH, -P(O)(OR<sub>30</sub>))OR<sub>31</sub>,

-P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub> -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or C(O)NH(R<sub>37</sub>);

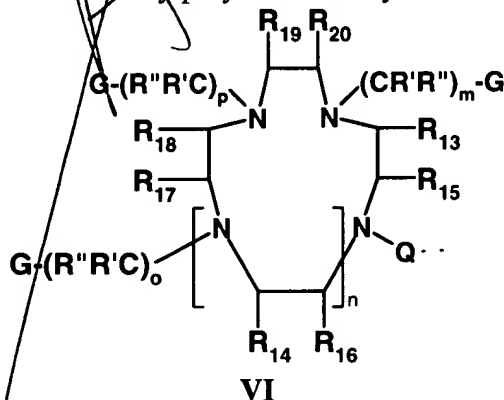
each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -  
hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R<sub>3</sub> through -R<sub>5</sub>, -R<sub>7</sub>, -R<sub>8</sub>, -R<sub>21</sub> through -R<sub>23</sub>, and -R<sub>25</sub> through -R<sub>27</sub> is  
independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -  
aryl, or -heterocyclo, each of which is optionally substituted;

each -R<sub>1</sub>, -R<sub>2</sub>, -R<sub>6</sub>, -R<sub>9</sub> through -R<sub>12</sub>, -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>37</sub> is independently -H, -  
alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen  
containing heterocycle;

or a pharmaceutically acceptable salt thereof.

19. The composition of claim 18 wherein M<sub>5</sub> is a paramagnetic or superparamagnetic  
metal and -K<sub>5</sub> is an enhanced relaxivity polyaza macrocyclic radical of formula VI:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

-Q- is  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$ ;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -  
N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or Y1

wherein Y1 is  $-C(=X5)-X6-W-$ ,

wherein W is a single bond, -alkylidene-, -cycloalkylidene-, -

arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is -H, -R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>))OH, -P(O)(OR<sub>30</sub>))OR<sub>31</sub>, -P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub> - C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or C(O)NH(R<sub>37</sub>);

each G is independently -C(O)OR<sup>'''</sup>, -P(O)(OR<sup>'''</sup>))OH, -P(O)(OR<sup>'''</sup>)<sub>2</sub>, -P(O)(OR<sup>'''</sup>)R<sup>'''</sup>, -P(O)(OH)R<sup>'''</sup> C(O)N(R<sup>'''</sup>)<sub>2</sub>, or C(O)NH(R<sup>'''</sup>);

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

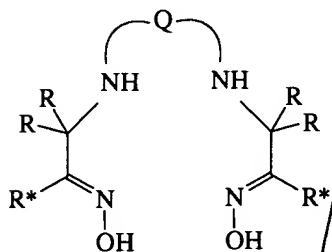
each -R<sub>13</sub> through -R<sub>23</sub>, and R<sub>25</sub> through -R<sub>27</sub> is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>37</sub> is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

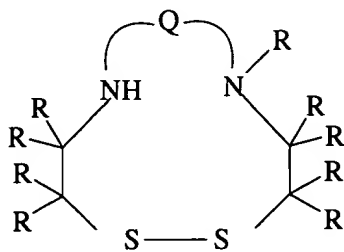
or R<sub>13</sub> together with R<sub>15</sub>, and R<sub>17</sub> together with R<sub>18</sub>, independently form, together with the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R<sub>13</sub> and R<sub>15</sub> are each hydrogen and R<sub>17</sub>, together with R<sub>18</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R<sub>13</sub>, together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen;

or a pharmaceutically acceptable salt thereof.

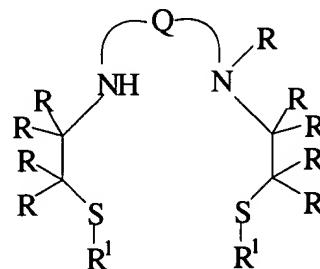
20. The compositions of claim 18 wherein -K<sub>5</sub> is a metal chelating polydentate ligand radical of formula IIIa - IIIc:



IIIa



IIIb



IIIc

wherein

Q is the group  $-(C(RR))_{m1}-Y^1(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}-$

wherein

$Y^1$  and  $Y^2$  are independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n is 0 or 1; and  $m1$ ,  $m2$  and  $m3$  are integers independently selected from 0 to 4, provided that the sum of  $m1$  and  $m2$  is greater than zero;

all R and  $R^*$  groups are independently  $-R^4$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OR^5$ ,  $-COOR^5$ ,  $-CON(R^5)_2$ ,  $-N(R^5)_2$ ,  $-alkyl-COOR^5$ ,  $-alkyl-C(O)-N(R^5)_2$ ,  $-alkyl-N(R^5)_2$ ,  $-C(O)OR^5$ ,  $-C(O)N(R^5)_2$ ,  $-aryl-N(R^5)_2$ ,  $acyl$ ,  $acyloxy$ ,  $heterocyclo$ ,  $hydroxyalkyl$ ,  $-SO_2-R^5$ ,  $-alkyl-SO_2-R^5$ , or  $-[R^3]-$ ;

wherein each  $-[R^3]-$  is, in its entirety, the linking group  $-[(A)p^*]-$  that serves to couple the metal chelating ligand radical  $-M_5$  to  $-X-$ ;

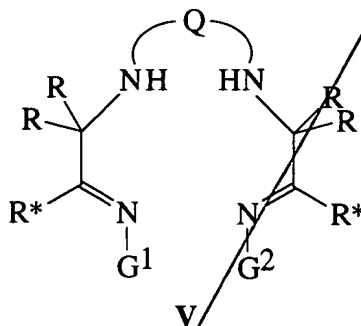
each  $-R^4$  is independently  $-H$ ,  $-alkyl$ ,  $-alkoxy$ ,  $-hydroxy$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted;

each  $-R^5$  is independently  $-H$ ,  $-alkyl$ ,  $-aryl$ ,  $-cycloalkyl$  or  $-hydroxyalkyl$ , each of which is independently substituted;

with the provisos that a carbon atom bearing an  $-R$  group is not directly bonded to more than one heteroatom; and that one to three R or  $R^*$  groups on  $-K_5$  is  $-[R^3]-$ ;

or a pharmaceutically acceptable salt thereof.

21. The compositions of claim 18 wherein  $-K_5$  is a polydentate metal-chelating ligand radical of formula V:



wherein

Q is the group  $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}-$ ;

$Y^1$  and  $Y^2$  are each independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n and  $n1$  are each independently 0 or 1; and  $m1$ ,  $m2$  and  $m3$  are independently 0 or an integer from 1 to 4; provided that  $m1$  and  $m2$  are not both 0, that  $m1 + m2 + n + n1$  is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each R and  $R^*$  group is independently:  $-H$ ,  $-R^4$ ,  $-alkoxy$ ,  $-hydroxy$ ,  $-halogen$ , especially fluoro,  $-haloalkyl$ ,  $-OR^5$ ,  $-C(O)-R^5$ ,  $-C(O)-N(R^5)_2$ ,  $-N(R^5)_2$ ,  $-N(R^5)-$



COR<sup>5</sup>, -alkyl-C(O)-OR<sup>5</sup>, -alkyl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, -alkyl-N(R<sup>5</sup>)<sub>2</sub>, -alkyl-N(R<sup>5</sup>)-COR<sup>5</sup>, -aryl-C(O)-OR<sup>5</sup>, -aryl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, -aryl-N(R<sup>5</sup>)<sub>2</sub>, -aryl-N(R<sup>5</sup>)-COR<sup>5</sup>, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, -arylalkyl, -SO<sub>2</sub>-R<sup>5</sup>, -alkyl-SO<sub>2</sub>-R<sup>5</sup>, or -[R<sup>3</sup>]-;

wherein

each  $-\text{[R}^3\text{]}-$  is, in its entirety, the linking group  $-\text{[(A)p}^*\text{]}-$  that serves to couple the metal chelating ligand radical  $\text{K}_5$  to  $-\text{X}-$ ;

each -R<sup>4</sup> is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R<sup>5</sup> is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted;

or

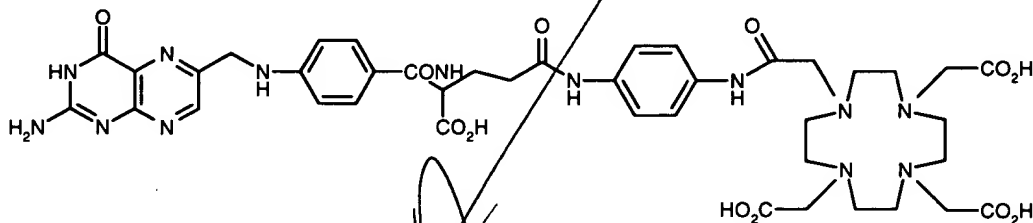
two R groups, or an R group and an R\* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R\* groups above;

each -G<sup>1</sup> and -G<sup>2</sup> is independently -OH or -(NR<sup>6</sup>)<sub>2</sub>; with the proviso that at least one of -G<sup>1</sup> or -G<sup>2</sup> is -(NR<sup>6</sup>)<sub>2</sub>, where each -R<sup>6</sup> is independently -hydrogen, -alkyl, -aryl, -acyl or -[R<sup>3</sup>]-; and

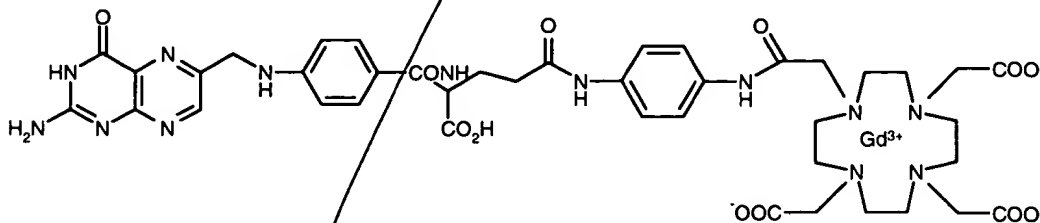
$A$  is a linking group; and  $p$  is 0 or a positive integer;

with the proviso that at one to three -R, -R\*, or -R<sup>6</sup> groups is -[R<sup>3</sup>]-; or a pharmaceutically acceptable salt thereof.

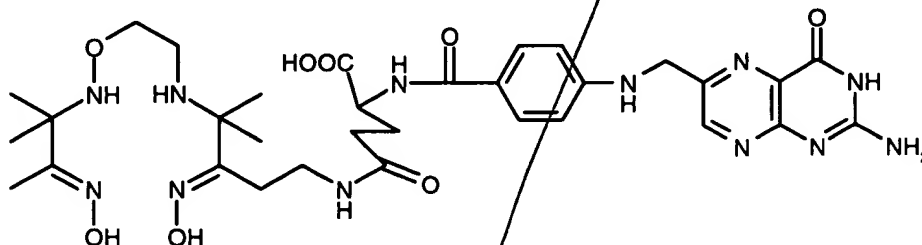
25 22. The composition of claim 18 wherein said folate-receptor binding ligand, N-Pteroyl- $\gamma$ -glutamyl-APADO3A, has the structure:



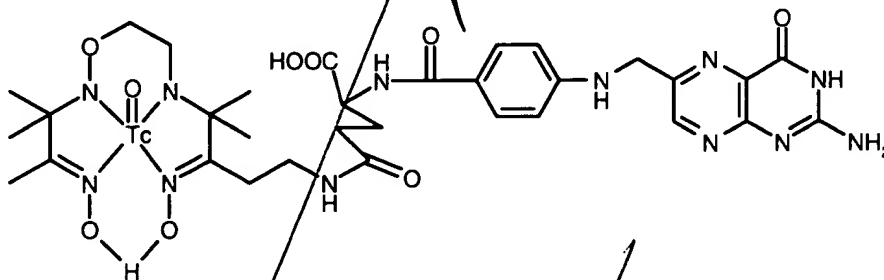
23. The composition of claim 18 containing the folate-receptor binding ligand Gd-  
30 DO3A-APA-( $\gamma$ )-folate, having the structure:



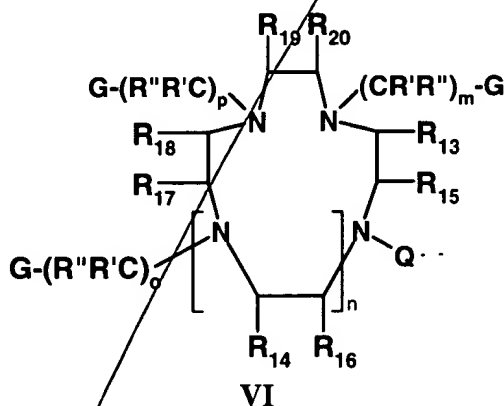
24. The composition of claim 18 containing the folate-receptor binding ligand 12-N-(N-Pteroyl- $\gamma$ -L-glutamyl)-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime, having the structure:



25. The composition of claim 18 containing the folate-receptor binding ligand Technetium oxo 12-N-(N-Pteroyl- $\gamma$ -L-glutamyl)-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecanedione dioxime, having the structure:



26. The composition of claim 18 wherein  $M_1$  or both  $M_1$  and  $M_5$  are paramagnetic or superparamagnetic metals and  $K_1$  or both  $-K_1$  and  $-K_5$  are enhanced relaxivity polyaza macrocyclic radicals of formula VI:



wherein

$n$  is 0 or 1;

each  $m$ ,  $o$ , and  $p$  is independently 1 or 2;

$Q$  is  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$ ;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

Y is a single bond, -C(R25)(R26)-, or Y1 wherein,

Y1 is -C(=X5)-X6-W-, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R27, -C(O)OR28, -P(O)(OR29))OH, -P(O)(OR30))OR31,

-P(O)(OR32)R33, -P(O)(OH)R34 -C(O)N(R35)(R36), or C(O)NH(R37);

each G is independently -C(O)OR''', -P(O)(OR''')OH, -P(O)(OR''')2,

-P(O)(OR''')R'', -P(O)(OH)R' C(O)N(R''')2, or C(O)NH(R''');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

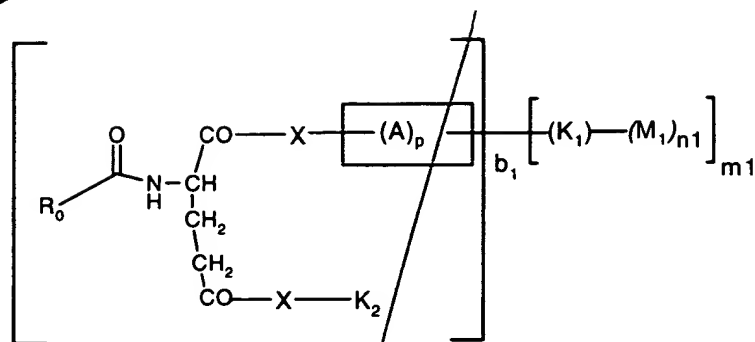
each -R13 through -R23, and R25 through -R27 is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, aryl, or -heterocyclo, each of which is optionally substituted;

each -R24, and -R28 through -R37 is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R13 and R15 are each hydrogen and R17, together with R18, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R13, together with R15, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R17 and R18 are hydrogen;

or a pharmaceutically acceptable salt thereof.

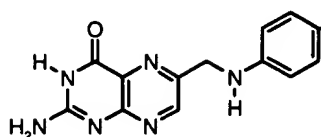
27. The composition for visualization or radiotherapy of tissues or organs that overexpress folate-binding protein using magnetic resonance imaging or neutron capture therapy techniques comprising one or more folate-receptor binding residues conjugated to one or more enhanced relaxivity polyaza macrocyclic radicals which are optionally chelated to a paramagnetic or superparamagnetic metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a radiotherapeutic effect using neutron capture therapy; wherein said folate-receptor binding compound has the structure of formula IIc:



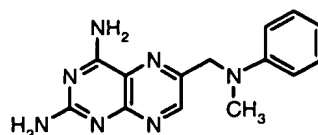
IIc

wherein

R<sub>0</sub> is a folate-receptor binding residue of formula:



or



each X is independently -O-, -S-, -NH-, or -NR<sub>1</sub>-;

n<sub>1</sub> and n<sub>5</sub> are independently 0 or 1;

b<sub>1</sub> and b<sub>5</sub> are independently 1 to 3;

m<sub>1</sub> and m<sub>5</sub> are independently 1 to 81;

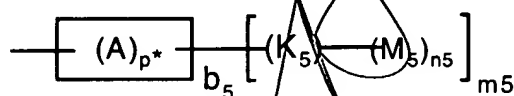
each -K<sub>1</sub> is independently

-H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R<sub>2</sub>)<sub>2</sub>, -glutamate, -polyglutamate, or -K<sub>4</sub>;

each -K<sub>2</sub> is independently

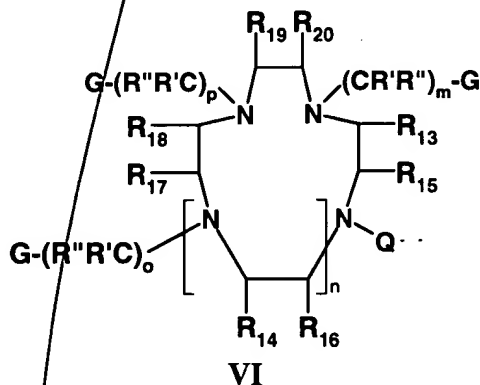
-H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R<sub>2</sub>)<sub>2</sub>, -glutamate, -polyglutamate, or -K<sub>3</sub>;

-K<sub>3</sub> is



M<sub>1</sub> and M<sub>5</sub> are paramagnetic or superparamagnetic metals; and

-K<sub>4</sub> and -K<sub>5</sub> are each independently enhanced-relaxivity polyaza macrocyclic metal-chelating ligand radicals of formula VI that are optionally chelated to M<sub>1</sub> and M<sub>5</sub>:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is  $-\text{C}(\text{R}')(\text{R}'')_{s1}-\text{C}(\text{t})(\text{R}_{21})_{s2}-\text{C}(\text{R}_{22})(\text{R}_{23})_{s3}-\text{X3}-\text{Y}-\text{X4}-$ ; wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or Y1,

wherein Y1 is  $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$ ,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>))OH, -P(O)(OR<sub>30</sub>))OR<sub>31</sub>,

-P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub> -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or

C(O)NH(R<sub>37</sub>);

each G is independently -C(O)OR''', -P(O)(OR''')OH, -P(O)(OR''')<sub>2</sub>,

-P(O)(OR''')R'', -P(O)(OH)R'' C(O)N(R''')<sub>2</sub>, or C(O)NH(R''');

each R' and R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R<sub>13</sub> through -R<sub>23</sub>, and -R<sub>25</sub> through -R<sub>27</sub> is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>37</sub> is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R<sub>13</sub> together with R<sub>15</sub>, and R<sub>17</sub> together with R<sub>18</sub>, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or

R<sub>13</sub> and R<sub>15</sub> are each hydrogen and R<sub>17</sub>, together with R<sub>18</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R<sub>13</sub>, together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen;

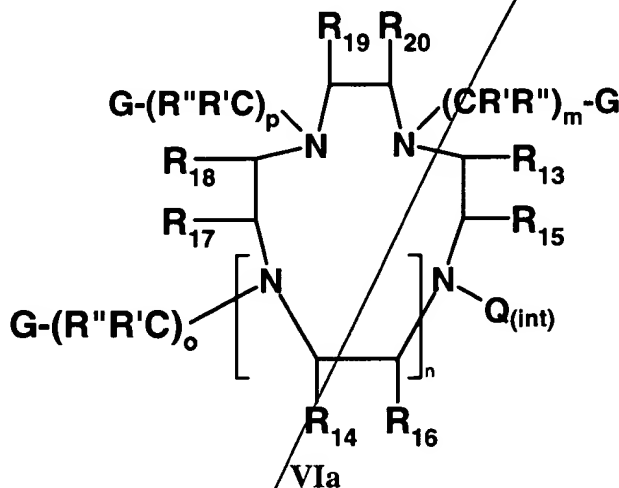
-(A)p- and -(A)p\*- are optional linkers each independently comprising a straight or branched chain made up of moieties that are the same or different and selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sub>3</sub>-, -CR<sub>4</sub>R<sub>5</sub>-, -CH=CH-, -CH=CR<sub>6</sub>-,

$>CR_7-CR_8<$ ,  $-C=C-$ ,  $-CR_9=CR_{10}-$ ,  $-C\equiv C-$ , -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ( $-CO-$ ),  $-O-$ ,  $-S-$ ,  $-NH-$ ,  $-HC=N-$ ,  $-CR_{11}=N-$ ,

$-NR_{12}-$ ,  $-CS-$ ,  $-\overset{\overset{H}{|}}{C}-$ ,  $-\overset{\overset{H}{|}}{C}-$ ,  $-\overset{\overset{H}{|}}{N}-$ ; and  
p and p\* are each individually 0 to 24;

or  $-X-[(A)p]-$  or  $-X-[(A)p^*]-$  in its entirety is the group  $-Q-$  as defined above  
each  $-R_3$  through  $-R_5$ ,  $-R_7$  and  $-R_8$  is independently  $-H$ , -alkyl, -alkenyl, -alkoxy, -aryl, a  
5- or 6-membered nitrogen or oxygen containing heterocycle, halogen, hydroxy or -  
hydroxyalkyl; and  
each  $-R_1$ ,  $-R_2$ ,  $-R_6$ ,  $-R_9$  through  $-R_{12}$  is independently  $-H$ , -alkyl, -alkoxy, -cycloalkyl, -  
aryl, -heterocyclo-, -hydroxy or -hydroxyalkyl;  
or a pharmaceutically acceptable salt thereof.

28. A conjugatable polyaza macrocyclic intermediate useful for the preparation of the  
composition of claim 27, said intermediate containing at least one free amine, carboxylate  
or thiocarboxylate functionality that can be used for conjugation to targeting vectors such as  
folate, said intermediates having the structure of formula VIa:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

$-Q(int)$  is a conjugatable amine-, carboxylate- or thiocarboxylate-containing group  
of formula  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X_3-Y-X_4$ ;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

$X_3$  is a single bond,  $-O-$ ,  $-S-$ ,  $-NH-$  or  $-NR_{24}-$  if Y is present,

or  $X_3$  is  $-OH$ ,  $-SH$ ,  $-NH_2$  or  $-N(R_{24})H$  if Y and  $X_4$  are absent;

$X_4$  is a single bond,  $-OH$ ,  $-COOH$ ,  $-SH$ ,  $-NHR_{24}$  or  $-NH_2$ ;

Y is a single bond,  $-C(R_{25})(R_{26})-$ , or Y1

wherein,

Y1 is  $-C(=X_5)-X_6-W-$ , wherein

X<sub>5</sub> is =O or =S;

X<sub>6</sub> is a single bond, -SH, -NH(R<sub>38</sub>), -NH<sub>2</sub> or -OH if W and X<sub>4</sub> are absent, and is -S-, -O-, -NH-, or -N(R<sub>39</sub>)-, if W and X<sub>4</sub> are present;

W is a single bond, or is -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is -H, -R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>))OH, -P(O)(OR<sub>30</sub>))OR<sub>31</sub>, -P(O)(OR<sub>32</sub>)R<sub>33</sub>, -

10 P(O)(OH)R<sub>34</sub> -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or -C(O)NH(R<sub>37</sub>);

each -G is independently -C(O)OR<sup>'''</sup>, -P(O)(OR<sup>'''</sup>)OH, -P(O)(OR<sup>'''</sup>)<sub>2</sub>, -P(O)(OR<sup>'''</sup>)R<sup>''</sup>, -P(O)(OH)R<sup>''</sup> -C(O)N(R<sup>'''</sup>)<sub>2</sub>, or -C(O)NH(R<sup>'''</sup>);

each -R' and -R<sup>''</sup> is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

15 each -R<sup>'''</sup> is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

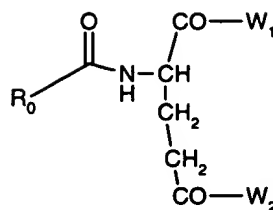
each -R<sub>13</sub> through -R<sub>23</sub>, and -R<sub>25</sub> through -R<sub>27</sub> is independently -H, -alkyl, alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

20 each -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>39</sub> is independently -H, -alkyl, -alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R<sub>13</sub> together with R<sub>15</sub>, and R<sub>17</sub> together with R<sub>18</sub>, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R<sub>13</sub> and R<sub>15</sub> are each hydrogen and R<sub>17</sub>, together with R<sub>18</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R<sub>13</sub>, together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen;

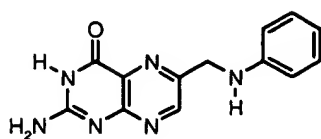
or a pharmaceutically acceptable thereof.

29. A composition comprising folate-receptor binding ligands and a pharmaceutically acceptable carrier for use nuclear medicine, magnetic resonance imaging, or neutron capture therapy techniques, said folate-receptor binding ligands comprising dendrimeric first-, second-, third-, and fourth- generation conjugates containing one folate-receptor binding residue coupled one or more macrocyclic metal-chelating ligand radicals that are optionally chelated to paramagnetic, superparamagnetic, radioactive or non-radioactive metals capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; wherein said folate-receptor binding compounds have the structure of formulae VIIa - VIId:

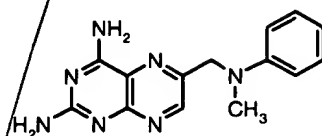


**VIIa - VIId**

wherein  $\text{R}_0$  is a folate-receptor binding residue of formula:



or

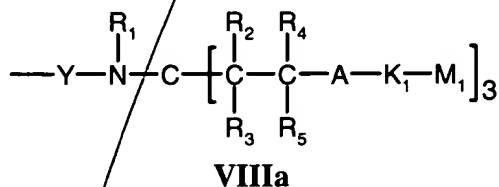


- 5 wherein for the first generation dendrimers of formula **VIIa**, bearing one folate-receptor binding residue and 3 or 6 metal chelating ligand radicals:

$\text{W}_1$  and  $\text{W}_2$  are each independently  $-\text{OR}''$ ,  $-\text{SR}''$ ,  $-\text{NR}''\text{R}''$ ,  $-\text{CON}(\text{R}_2)_2$ , -glutamate, -polyglutamate, or  $-\text{K}_6$ ;

wherein each  $-\text{R}''$  is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo;

- 10 with the proviso that either  $\text{W}_1$ ,  $\text{W}_2$ , or both  $\text{W}_1$  and  $\text{W}_2$  of formula **VIIa** must be  $-\text{K}_6$ , where  $-\text{K}_6$  is a residue of formula **VIIIa**:



wherein

- 15 Y is a single bond or  $-\text{Y}'-\text{C}(=\text{X})-$

wherein

X is  $=\text{O}$  or  $=\text{S}$ ;

$\text{Y}'$  is  $\text{N}(\text{R}_6)-\text{Z}-$ ;

wherein

- 20 Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is  $-\text{C}(=\text{O})-$ ,  $\text{C}(=\text{S})$ , or  $-\text{CH}_2-\text{N}(\text{R}_7)-$ ;

$\text{M}_1$  is a superparamagnetic, paramagnetic, radioactive or non-radioactive metal, and

$\text{K}_1$  is a macrocyclic metal chelating ligand residue;

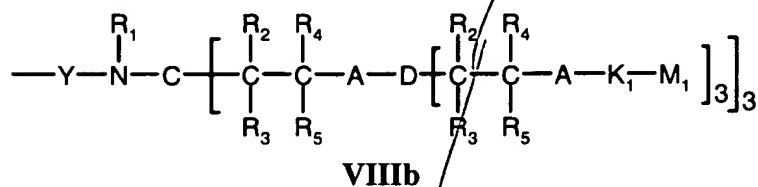
- 25 and,

wherein for second generation dendrimers, bearing one folate receptor binding residue and 9 or 18 macrocyclic metal-chelating ligand radicals and having the structure of formula **VIIb**:

$\text{W}_1$  and  $\text{W}_2$  are each independently  $-\text{OR}''$ ,  $-\text{SR}''$ ,  $-\text{NR}''\text{R}''$ , or  $-\text{K}_7$ ,



wherein each -R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo, and -K<sub>7</sub> is a residue of formula **VIIIb**; with the proviso that either W<sub>1</sub>, W<sub>2</sub>, or both W<sub>1</sub> and W<sub>2</sub> must be -K<sub>7</sub>



wherein

Y is a single bond or -Y'-C(=X)-

wherein X is =O or =S and Y' is -N(R<sub>6</sub>)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, C(S)-, or -CH<sub>2</sub>-N(R<sub>7</sub>)-;

D is -N(R<sub>6</sub>)-C- if A is -C(O)- or -C(S)- or -C(=X<sub>2</sub>)-E-N(R<sub>7</sub>)-C- if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-;

wherein

E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X<sub>2</sub> is =O or =S;

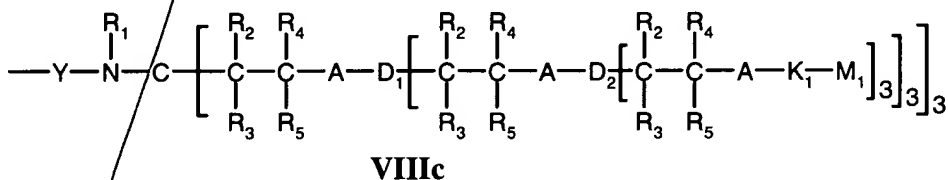
and wherein

for the third generation dendrimeric compounds of formula **VIIc**; bearing one folate receptor binding residue and 27 or 54 macrocyclic metal-chelating ligand radicals:

W<sub>1</sub> and W<sub>2</sub> are each independently -OR''', -SR''', -NR'''R''', or -K<sub>8</sub>

wherein each -R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo, and -K<sub>8</sub> is a residue of formula **VIIIc**;

with the proviso that either W<sub>1</sub>, W<sub>2</sub>, or both W<sub>1</sub> and W<sub>2</sub> of the compounds of formula **VIIc** must be -K<sub>8</sub> :



wherein,

Y is a single bond or -Y'-C(=X)-

wherein

X is =O or =S;

Y' is -N(R<sub>6</sub>)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, -C(S)-, or -CH<sub>2</sub>-N(R<sub>7</sub>)-;

D<sub>1</sub> and D<sub>2</sub> are each independently -N(R<sub>6</sub>)-C if A is -C(O)- or -C(S)-, and -C(=X<sub>2</sub>)-E-N(R<sub>7</sub>)-C if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-;

wherein

E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X<sub>2</sub> is =O or =S;

and

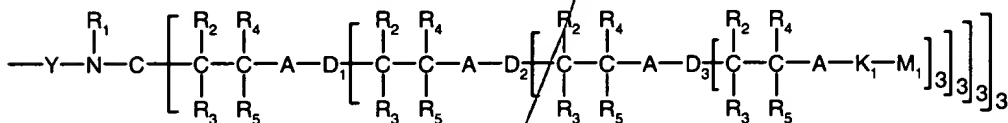
wherein for the fourth generation dendrimeric compounds of formula **VIIId**; bearing one folate receptor binding residue and 81 or 162 macrocyclic metal-chelating ligand radicals:

W<sub>1</sub> and W<sub>2</sub> are each independently -OR<sup>'''</sup>, -SR<sup>'''</sup>, -NR<sup>'''</sup>R<sup>'''</sup> or -K<sub>9</sub>,

wherein each R<sup>'''</sup> is independently -H, -alkyl, -aryl, -cycloalkyl, -

hydroxyalkyl, or -heterocyclo and -K<sub>9</sub> is a residue of formula **VIIIId**;

with the proviso that either W<sub>1</sub>, W<sub>2</sub>, or both W<sub>1</sub> and W<sub>2</sub> of the compounds of formula **VIIId** must be -K<sub>9</sub> ):



wherein Y is a single bond or -Y'-C(=X)-

wherein

X is =O or =S;

Y' is -N(R<sub>6</sub>)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, -C(S)-, or -CH<sub>2</sub>-N(R<sub>7</sub>)-;

D<sub>1</sub>, D<sub>2</sub>, and D<sub>3</sub> are each independently -N(R<sub>6</sub>)-C if A is -C(O)- or C(S)-, and -C(=X<sub>2</sub>)-E-N(R<sub>7</sub>)-C if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-;

wherein E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X<sub>2</sub> is =O or =S; and

each -R<sub>1</sub> to -R<sub>7</sub> of the compounds of formula **VIIIa-VIIId** is independently -H, -alkyl, -hydroxyalkyl, -alkoxy, -alkoxyalkyl, -cycloalkyl, or -aryl; each of which is optionally substituted,

or a pharmaceutically acceptable salt thereof.

30. The composition of claim 29 wherein W<sub>1</sub> of formula **VIIa - VIIId** is a residue of formula **VIIIa, VIIIb, VIIIc or VIIIId**;

and

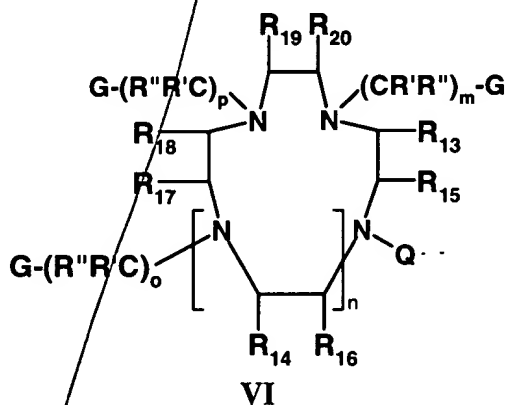
W<sub>2</sub> of formula **VIIa - VIIId** is -OR<sup>'''</sup>, -SR<sup>'''</sup>, -NR<sup>'''</sup>R<sup>'''</sup> -CON(R<sub>2</sub>)<sub>2</sub>, -glutamate, or -

polyglutamate, wherein each R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo.

31. The composition of claim 29 wherein W<sub>2</sub> of formula VIIa - VIId is a residue of formula VIIIa, VIIIb, VIIIc or VIId;  
and W<sub>1</sub> of formula VIIa - VIId is -OR''', -SR''', -NR'''R''', -CON(R<sub>2</sub>)<sub>2</sub>, -glutamate, or -polyglutamate, wherein each R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo.

32. The dendrimeric compositions of claim 29 wherein both W<sub>1</sub> and W<sub>2</sub> of formula VIIa - VIId is a residue of formula VIIIa, VIIIb, VIIIc or VIId.

33. The dendrimeric folate-receptor binding compositions of formula VIIa - VIId of claim 29 for use in diagnostic imaging using magnetic resonance or nuclear medicine techniques, or for use in radiation- or neutron-capture therapy, wherein M<sub>1</sub> is a radioactive-, paramagnetic- or superparamagnetic- metal and each K<sub>1</sub> is a macrocyclic metal chelating ligand radical of formula VI:



wherein said metal chelating radical is attached to the remainder of the compound of formulae VIIa - VIId via the free -N(R)- atom of the function -Q- if A is -C(O)- or -C(S)- or through the free -C(O)- atom of the function -Q- if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-;

wherein -Q- is -[C(R')(R'')]s<sub>1</sub>-[C(t)(R<sub>21</sub>)s<sub>2</sub>]-[C(R<sub>22</sub>)(R<sub>23</sub>)s<sub>3</sub>]-X<sub>3</sub>-Y-X<sub>4</sub>-;

wherein

s<sub>1</sub>, s<sub>2</sub>, s<sub>3</sub>, and s<sub>4</sub> are independently 0 to 2;

X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> are independently a single bond, -O-, -S-, or -N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or Y<sub>1</sub>,

wherein Y<sub>1</sub> is -C(=X<sub>5</sub>)-X<sub>6</sub>-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>))OH, -P(O)(OR<sub>30</sub>))OR<sub>31</sub>, -P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub>, -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or C(O)NH(R<sub>37</sub>);

each G is independently -C(O)OR<sup>'''</sup>, -P(O)(OR<sup>'''</sup>)OH, -P(O)(OR<sup>'''</sup>)<sub>2</sub>, -P(O)(OR<sup>'''</sup>)R<sup>''</sup>, -P(O)(OH)R<sup>''</sup>, C(O)N(R<sup>'''</sup>)<sub>2</sub>, or C(O)NH(R<sup>'''</sup>);

each R' and R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

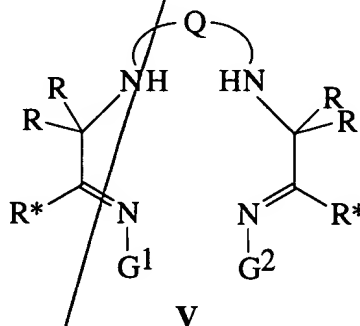
each R<sup>'''</sup> is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R<sub>13</sub> through -R<sub>23</sub>, and -R<sub>25</sub> through -R<sub>27</sub> is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>37</sub> is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or a pharmaceutically accepted salt thereof.

34. The dendrimeric folate receptor binding composition of formula VIIa - VIId of claim 29 wherein M<sub>1</sub> is a radioactive metal and at least one -K<sub>1</sub> is a macrocyclic metal chelating ligand radical of formula V:



wherein

-Q- is the group -(C(RR))<sub>m1</sub>-(Y<sup>1</sup>)<sub>n</sub>-(C(RR))<sub>m2</sub>-(Y<sup>2</sup>-(C(RR))<sub>m3</sub>)<sub>n1</sub>;

Y<sup>1</sup> and Y<sup>2</sup> are each independently -CH<sub>2</sub>-, -NR-, -O-, -S-, -SO-, -SO<sub>2</sub>- or -Se-;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that m1 + m2 + n + n1 is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and -R\* group is independently: -R<sup>4</sup>; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl, -OR<sup>5</sup>, -C(O)-R<sup>5</sup>, -C(O)-N(R<sup>5</sup>)<sub>2</sub>, -N(R<sup>5</sup>)<sub>2</sub>, -N(R<sup>5</sup>)-COR<sup>5</sup>, -alkyl-C(O)-OR<sup>5</sup>, -alkyl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, -alkyl-N(R<sup>5</sup>)<sub>2</sub>-, -alkyl-N(R<sup>5</sup>)-COR<sup>5</sup>, -aryl-C(O)-OR<sup>5</sup>, -aryl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, aryl-N(R<sup>5</sup>)<sub>2</sub>-, -aryl-N(R<sup>5</sup>)-COR<sup>5</sup>, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl, -SO<sub>2</sub>-R<sup>5</sup>, -alkyl-SO<sub>2</sub>-R<sup>5</sup>, or -[R<sup>3</sup>]-;

wherein

-[R<sup>3</sup>]- is a linking group -[(A)p]- that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae

**VIIa through VIId;**

wherein  $-(A)_p-$  comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of:  $-CH_2-$ ,  $-CHR_3-$ ,  $-CR_4R_5-$ ,  $-CH=CH-$ ,  $-CH=CR_6-$ ,  $>CR_7-CR_8<$ ,  $-C=C-$ ,  $-CR_9=CR_{10}-$ ,  $-C\equiv C-$ , -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ( $-CO-$ ),  $-O-$ ,  $-S-$ ,

$-NH-$ ,  $-HC=N-$ ,  $-CR_{11}=N-$ ,  $-NR_{12}-$ ,  $(-CS-)$ ,  $-\overset{H}{\underset{|}{C}}-$ ,  $-\overset{H}{\underset{|}{C}}-$ ,  $-\overset{H}{\underset{|}{N}}-$ , and

p is an integer from 0 to 24;

each  $-R^4$  and  $-R_3$  through  $-R_5$  is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each  $-R^5$  and  $-R_6$  through  $-R_{12}$  is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

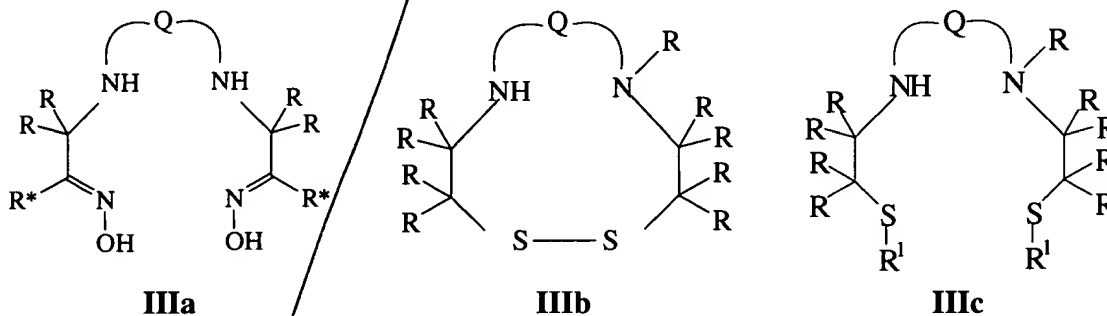
two R groups, or an R group and an  $R^*$  group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or  $R^*$  groups above;

each  $-G^1$  and  $-G^2$  is independently  $-OH$  or  $-(NR^6)_2$ ; with the proviso that at least one of  $-G^1$  or  $-G^2$  is  $-(NR^6)_2$ , and each  $-R^6$  is independently -hydrogen, -alkyl, -aryl, -acyl or  $-[R^3]-$ ;

with the proviso that at least one  $-R$ ,  $-R^*$ , or  $-R^6$  group is  $-[R^3]-$ ;

or a pharmaceutically acceptable salt thereof.

35. The dendrimeric folate-receptor binding composition of formula **VIIa - VIId** of claim 29 for use in nuclear medicine or radiotherapy wherein  $M_1$  is a radioactive isotope and at least one  $K_1$  is a macrocyclic metal chelating ligand of formula **IIIa - IIIc**:



wherein

Q is the group  $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$ ,

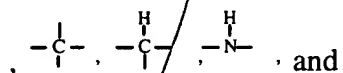
wherein

$Y^1$  and  $Y^2$  are independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n is 0 or 1; and m<sub>1</sub>, m<sub>2</sub> and m<sub>3</sub> are integers independently selected from 0 to 4, provided that the sum of m<sub>1</sub> and m<sub>2</sub> is greater than zero; all R and R\* groups are independently -R<sup>4</sup>, -Cl, -F, -Br, -OR<sup>5</sup>, -COOR<sup>5</sup>, -CON(R<sup>5</sup>)<sub>2</sub>, -N(R<sup>5</sup>)<sub>2</sub>, -alkyl-COOR<sup>5</sup>, -alkyl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, -alkyl-N(R<sup>5</sup>)<sub>2</sub>, -C(O)OR<sup>5</sup>, -C(O)N(R<sup>5</sup>)<sub>2</sub>, -aryl-N(R<sup>5</sup>)<sub>2</sub>, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -SO<sub>2</sub>-R<sup>5</sup>, -alkyl-SO<sub>2</sub>-R<sup>5</sup>, or -[R<sup>3</sup>]-;

wherein

-[R<sup>3</sup>]- is a linking group -[(A)p]- that links the metal chelating ligand of formula **IIIa**, **IIIb**, or **IIIc** to the remainder of the molecule; wherein -[(A)p]- comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sub>3</sub>-, -CR<sub>4</sub>R<sub>5</sub>-, -CH=CH-, -CH=CR<sub>6</sub>-, >CR<sub>7</sub>-CR<sub>8</sub><, -C=C-, -CR<sub>9</sub>=CR<sub>10</sub>-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl -(CO)-, -O-, -S-, -NH-, -HC=N-, -CR<sub>11</sub>=N-, -NR<sub>12</sub>-, and -(CS)-



p is an integer from 0 to 24;

each -R<sup>4</sup> and -R<sub>3</sub> through -R<sub>5</sub> is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

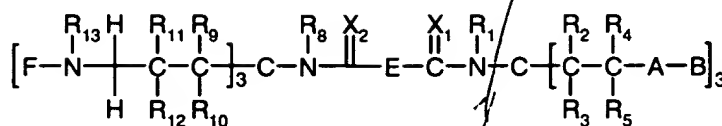
each -R<sup>5</sup> and -R<sub>6</sub> through -R<sub>12</sub> is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted;

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom; and that at least one -R or -R\* group on -K<sub>1</sub> is -[R<sup>3</sup>]-

or a pharmaceutically acceptable salt thereof.

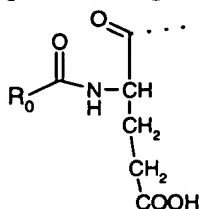
36. A folate-receptor binding ligand comprising dendrimeric first-, second-, third-, and fourth- generation conjugates containing one or more folate-receptor binding residues coupled to one or more macrocyclic metal-chelating ligand radicals that are capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect, wherein said folate-receptor binding ligands have the structure of formulae **IXa**, **IXb**, **IXc**, and **IXd**, representing dendrimers of generations 1, 2, 3, and 4, respectively,

wherein for the first generation dendrimers of formula **IXa**, bearing three folate and three metal chelating ligand radicals;

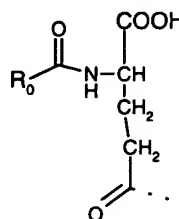


IXa

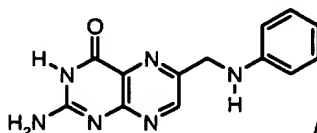
F is a folate-receptor binding residue of formula:



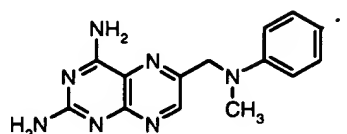
/or



wherein R<sub>0</sub> is a residue of formula:



or



each  $X_1$  through  $X_4$  is independently =O or =S;

each A is -C(O)-, -C(S)-, or -CH<sub>2</sub>-N(R<sub>7</sub>)-;

E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

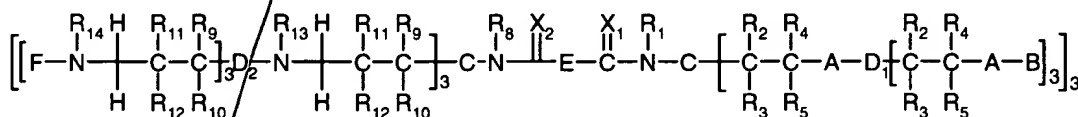
B is a macrocyclic metal-chelating ligand radical that is attached to A via an amide or thioamide bond and is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal;

-R<sub>1</sub>, -R<sub>6</sub> through -R<sub>8</sub>, -R<sub>13</sub>, and -R<sub>14</sub> are independently -H, -alkyl, -hydroxyalkyl, -cycloalkyl, or -aryl;

-R<sub>2</sub> through -R<sub>5</sub> and -R<sub>9</sub> through -R<sub>12</sub> are independently -H, -alkyl, -hydroxyalkyl, -alkoxy, -hydroxyalkyl, -halogen, -cycloalkyl, -aryl or -heterocyclo;

or a pharmaceutically accepted salt thereof;

and wherein for the second generation dendrimeric compounds of formula **IXb**, bearing nine folate-receptor binding residues and nine metal-chelating ligand radicals:

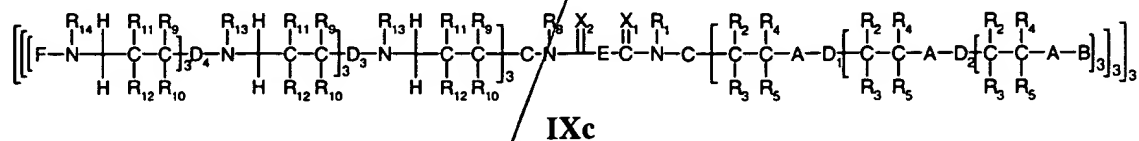


IXb

A, B, E, F, X<sub>1</sub> through X<sub>4</sub> and all -R groups are as defined for the compounds of formula **IXa**:

D<sub>1</sub> and D<sub>2</sub> are independently -N(R<sub>6</sub>)-C if A is -C(O)- or -C(S)-, and -C(=X<sub>3</sub>)-E-N(R<sub>7</sub>)-C if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-;

and wherein for the third generation dendrimeric compounds of formula **IXc**, bearing 27 folate receptor binding residues and 27 metal chelating ligand radicals;



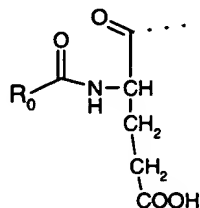
- 5 D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> are independently -N(R<sub>6</sub>)-C if A is -C(O)- or -C(S)-, and -C(=X<sub>3</sub>)-E-N(R<sub>7</sub>)-C if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-; and all other groups are defined as above;



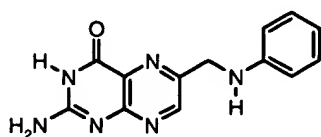
[illegible]

D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub>, and D<sub>6</sub> are each independently  $-N(R_6)-C$  if A is  $-C(O)-$  or  $-C(S)-$ , and  $-C(=X_3)-E-N(R_7)-C$  if A is  $-\text{CH}_2-N(R_7)-$ ;

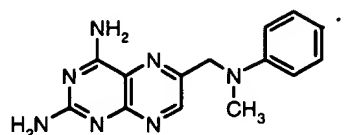
37. The dendrimeric composition of claim 36 wherein F of formulae **IXa**, **IXb**, **IXc**, and **IXd** is a folate-receptor binding residue of formula:



wherein  $\text{R}_0$  is a residue of formula:

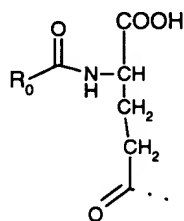


or

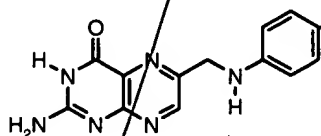


or a pharmaceutically acceptable salt thereof.

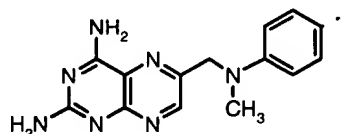
38. The dendrimeric folate-receptor binding composition of claim 36 wherein F of formulae **IXa**, **IXb**, **IXc**, and **IXd** is a folate receptor binding residue of formula:



wherein  $\text{R}_0$  is a residue of formula:

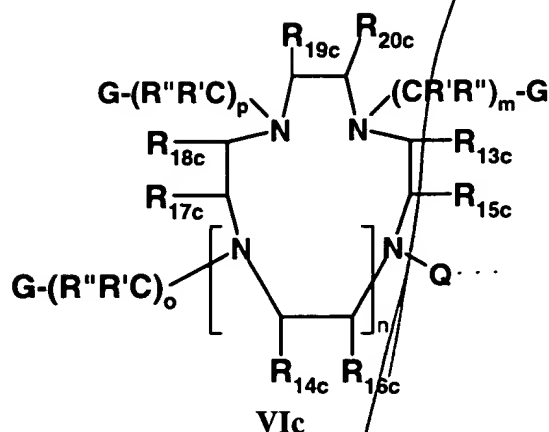


or



or a pharmaceutically acceptable salt thereof.

39. The folate-receptor binding composition of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim 36, wherein B is a polyaza macrocyclic ligand radical of formula **VIc** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal,



wherein said macrocyclic ligand radical is attached to A via an amide or thioamide linkage through a free N atom of the function -Q- if A is -C(O)- or -C(S)- or through a free -C(O)- group of the function -Q- if A is -CH<sub>2</sub>-N(R<sub>7</sub>)-;

-Q- is -[C(R')(R'')]s<sub>1</sub>-[C(t)(R<sub>21</sub>)]s<sub>2</sub>-[C(R<sub>22</sub>)(R<sub>23</sub>)]s<sub>3</sub>-X<sub>3</sub>-Y-X<sub>4</sub>-;

wherein

s<sub>1</sub>, s<sub>2</sub>, s<sub>3</sub>, and s<sub>4</sub> are independently 0 to 2;

-X<sub>3</sub>, -X<sub>4</sub>, -X<sub>5</sub>, and -X<sub>6</sub> are independently a single bond, -O-, -S-, or -N(R<sub>24</sub>)-;

Y is a single bond, -C(R<sub>25</sub>)(R<sub>26</sub>)-, or Y<sub>1</sub>,

wherein Y<sub>1</sub> is -C(=X<sub>5</sub>)-X<sub>6</sub>-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R<sub>27</sub>, -C(O)OR<sub>28</sub>, -P(O)(OR<sub>29</sub>)OH, -P(O)(OR<sub>30</sub>)OR<sub>31</sub>, -P(O)(OR<sub>32</sub>)R<sub>33</sub>, -P(O)(OH)R<sub>34</sub>, -C(O)N(R<sub>35</sub>)(R<sub>36</sub>), or C(O)NH(R<sub>37</sub>);

each G is independently -C(O)OR''', -P(O)(OR''')OH, -P(O)(OR''')<sub>2</sub>, -P(O)(OR''')R'', -P(O)(OH)R'' -C(O)N(R''')<sub>2</sub>, or -C(O)NH(R''');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

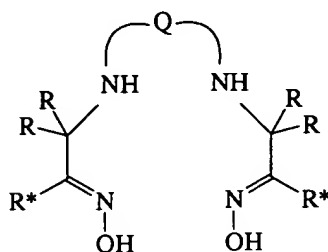
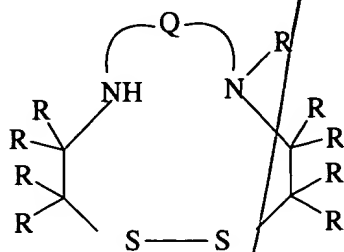
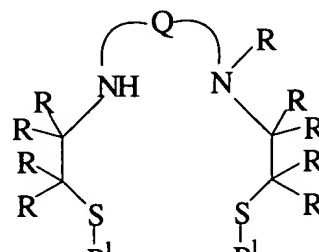
each -R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R<sub>13c</sub> through -R<sub>20c</sub>, -R<sub>21</sub> through -R<sub>23</sub>, and -R<sub>25</sub> through -R<sub>27</sub> is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>37</sub> is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen-containing heterocycle, each of which is optionally substituted;

or a pharmaceutically accepted salt thereof.

40. The dendrimeric folate-receptor binding composition of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim 36 wherein B is a metal-chelating ligand radical of formula **IIIa** - **IIIc** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal:


**IIIa**

**IIIb**

**IIIc**

wherein

Q is the group  $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$ ,

wherein

$Y^1$  and  $Y^2$  are independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n is 0 or 1; and m1, m2 and m3 are integers independently selected from 0 to 4, provided that the sum of m1 and m2 is greater than zero;

all R and R\* groups are independently  $-R^4$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OR^5$ ,  $-COOR^5$ ,  $-CON(R^5)_2$ ,  $-N(R^5)_2$ ,  $-alkyl-COOR^5$ ,  $-alkyl-C(O)-N(R^5)_2$ ,  $-alkyl-N(R^5)_2$ ,  $-C(O)OR^5$ ,  $-C(O)N(R^5)_2$ ,  $-aryl-N(R^5)_2$ ,  $-acyl$ ,  $-acyloxy$ ,  $-heterocyclo$ ,  $-hydroxyalkyl$ ,  $-SO_2-R^5$ ,  $-alkyl-SO_2-R^5$ , or  $-[R^3]-$ ;

wherein  $-[R^3]-$  is a linking group  $-[(A)p]-$  that couples the metal chelating radical of formula **IIIa**, **IIIb**, or **IIIc** to the remainder of the molecule;

$-[(A)p]-$  comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of:  $-CH_2-$ ,  $-CHR_3-$ ,  $-CR_4R_5-$ ,  $-CH=CH-$ ,  $-CH=CR_6-$ ,  $>CR_7-CR_8<$ ,  $-C=C-$ ,  $-CR_9=CR_{10}-$ ,  $-C\equiv C-$ ,  $-cycloalkylidene-$ ,  $-cycloalkenyl-$ ,  $-arylidene-$ ,  $-heterocyclo-$ ,  $-carbonyl$   $-(CO)-$ ,  $-O-$ ,  $-S-$ ,  $-NH-$ ,  $-HC=N-$ ,  $-CR_{11}=N-$ ,  $-$

$NR_{12}-$ ,  $-CS-$ ,  $-C(=O)-$ ,  $-C(=O)-$ ,  $-C(=O)-$ , and

p is an integer from 0 to 24;

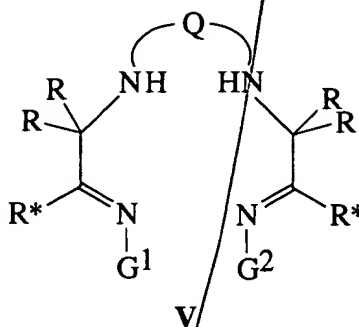
each  $-R^4$  and  $-R_3$  through  $-R_5$  is independently  $-H$ ,  $-alkyl$ ,  $-alkoxy$ ,  $-hydroxy$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted;

each  $-R^5$  and  $-R_6$  through  $R_{12}$  is independently  $-H$ ,  $-alkyl$ ,  $-aryl$ ,  $-cycloalkyl$  or  $-hydroxyalkyl$ , each of which is independently substituted;

and all other groups are defined as in claim 35,

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom; and that at least one -R or -R\* group on the metal chelating radical -K<sub>1</sub> of formulae **IIIa**, **IIIb**, or **IIIc** is -[R<sup>3</sup>]-; or a pharmaceutically acceptable salt thereof.

41. The dendrimeric folate-receptor binding composition of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim 36, wherein B is a metal-chelating ligand radical of formula V that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal:



wherein

-Q- is the group  $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2)-(C(RR))_{m3}n1$ ;

Y<sup>1</sup> and Y<sup>2</sup> are each independently -CH<sub>2</sub>-, -NR-, -O-, -S-, -SO-, -SO<sub>2</sub>- or -Se-;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that m1 + m2 + n + n1 is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and -R\* group is independently: -R<sup>4</sup>; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl, -OR<sup>5</sup>, -C(O)-R<sup>5</sup>, -C(O)-N(R<sup>5</sup>)<sub>2</sub>, -N(R<sup>5</sup>)<sub>2</sub>, -N(R<sup>5</sup>)-COR<sup>5</sup>, -alkyl-C(O)-OR<sup>5</sup>, -alkyl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, -alkyl-N(R<sup>5</sup>)<sub>2</sub>-, -alkyl-N(R<sup>5</sup>)-COR<sup>5</sup>, -aryl-C(O)-OR<sup>5</sup>, -aryl-C(O)-N(R<sup>5</sup>)<sub>2</sub>, aryl-N(R<sup>5</sup>)<sub>2</sub>-, -aryl-N(R<sup>5</sup>)-COR<sup>5</sup>, -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl, -SO<sub>2</sub>-R<sup>5</sup>, -alkyl-SO<sub>2</sub>-R<sup>5</sup>, or -[R<sup>3</sup>]-;

wherein

-[R<sup>3</sup>]- is a linking group -[(A)p]- that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae **IXa**, **IXb**, **IXc**, and **IXd**;

wherein -[(A)p]- comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: -CH<sub>2</sub>-, -CHR<sub>3</sub>-, -CR<sub>4</sub>R<sub>5</sub>-, -CH=CH-, -CH=CR<sub>6</sub>-, >CR<sub>7</sub>-CR<sub>8</sub><-, -C=C-, -CR<sub>9</sub>=CR<sub>10</sub>-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-,

-NH-, -HC=N-, -CR<sub>11</sub>=N-, -NR<sub>12</sub>-, (-CS-),  $-\overset{\text{H}}{\underset{|}{\text{C}}}-$ ,  $-\overset{\text{H}}{\underset{|}{\text{C}}}-$ ,  $-\overset{\text{H}}{\underset{|}{\text{N}}}-$ , and

p is an integer from 0 to 24;

each  $-R^4$  and  $-R_3$  through  $-R_5$  is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each  $-R^5$  and  $-R_6$  through  $-R_{12}$  is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

two R groups, or an R group and an  $R^*$  group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or  $R^*$  groups above;

each  $-G^1$  and  $-G^2$  is independently -OH or  $-(NR^6)_2$ ; with the proviso that at least one of  $-G^1$  or  $-G^2$  is  $-(NR^6)_2$ , and each  $-R^6$  is independently -hydrogen, -alkyl, -aryl, -acyl or  $-[R^3]$ ;

and all other groups are defined as in claim 80,

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom and that at least one -R,  $-R^*$ , or  $-R^6$  group on the metal chelating radical  $-K_1$  of formula V is  $-[R^3]$ ;

or a pharmaceutically acceptable salt thereof.

42. The diagnostic or radiotherapeutic composition of formula II of claim 2, wherein  $K_1$  is chelated to a radioactive, paramagnetic or superparamagnetic metal and  $K_2$  is other than  $-K_3$ .

43. The radiodiagnostic or radiotherapeutic composition of claim 2 wherein both  $K_1$  and  $K_5$  of formula II are metal-chelating ligand radicals that are chelated to a radioactive metal.

44. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using Nuclear Medicine imaging techniques, wherein either  $K_1$ , or both  $K_1$  and  $K_5$  is chelated to a radioisotope of technetium, indium, copper, ruthenium, gallium or gadolinium.

45. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein either  $K_1$ , or both  $K_1$  and  $K_5$  is chelated to a paramagnetic or superparamagnetic metal.

46. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein either  $K_1$ , or both  $K_1$  and  $K_5$  is chelated to gadolinium.

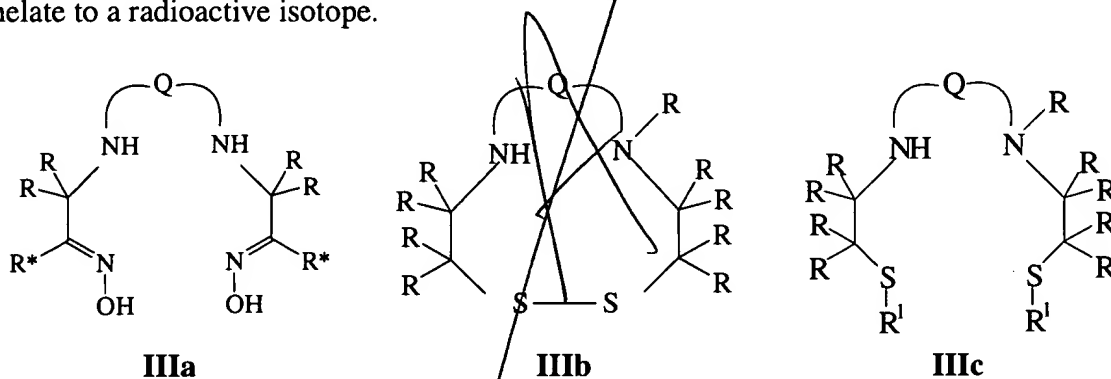
47. The diagnostic composition of claim 2 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein  $K_1$  is chelated to a paramagnetic or superparamagnetic metal and  $K_2$  is other than  $-K_3$ .

48. The diagnostic composition of claim 2 for use in Magnetic Resonance imaging applications, wherein said paramagnetic metal is selected from the group consisting of: chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III).

49. The diagnostic composition of claim 2, for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein  $K_1$  is chelated to gadolinium.

50. The radiotherapeutic composition of claim 2, for radiotherapy of tissues that overexpress folate binding protein, wherein either  $K_1$  or both  $K_1$  and  $K_5$  is chelated to a radioisotope selected from the group consisting of  $^{153}\text{Samarium}$ ,  $^{156}\text{Holmium}$ ,  $^{165}\text{Dysprosium}$ ,  $^{203}\text{Lead}$ ,  $^{186}\text{Rhenium}$ ,  $^{188}\text{Rhenium}$ ,  $^{88}\text{Yttrium}$ ,  $^{90}\text{Yttrium}$ ,  $^{211}\text{Bismuth}$ ,  $^{212}\text{Bismuth}$ ,  $^{213}\text{Bismuth}$ , and  $^{214}\text{Bismuth}$ .

51. The radiodiagnostic or radiotherapeutic composition of claim 2 wherein either  $K_1$ , or both  $K_1$  and  $K_5$  is a metal-chelating ligand radical of formula IIIa, IIIb, IIIc, that can chelate to a radioactive isotope.



wherein

Q is the group  $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$ ,

wherein

$Y^1$  and  $Y^2$  are independently  $-\text{CH}_2-$ ,  $-\text{NR}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}-$ ,  $-\text{SO}_2-$  or  $-\text{Se}-$ ;

$n$  is 0 or 1; and  $m_1$ ,  $m_2$  and  $m_3$  are integers independently selected from 0 to 4, provided that the sum of  $m_1$  and  $m_2$  is greater than zero;

all R and  $R^*$  groups are independently  $-\text{R}^4$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OR}^5$ ,  $-\text{COOR}^5$ ,  $-\text{CON}(\text{R}^5)_2$ ,  $-\text{N}(\text{R}^5)_2$ ,  $-\text{alkyl-COOR}^5$ ,  $-\text{alkyl-C(O)-N}(\text{R}^5)_2$ ,  $-\text{alkyl-N}(\text{R}^5)_2$ ,  $-\text{C(O)OR}^5$ ,  $-\text{C(O)N}(\text{R}^5)_2$ ,  $-\text{aryl-N}(\text{R}^5)_2$ , acyl, acyloxy, heterocyclo, hydroxyalkyl,  $-\text{SO}_2-\text{R}^5$ ,  $-\text{alkyl-SO}_2-\text{R}^5$ , or  $-\text{[R}^3]-$ ;

wherein  $-\text{[R}^3]-$  is a linking group  $-\text{[(A)p]}-$  that couples the metal chelating radical of formula IIIa, IIIb, or IIIc to the remainder of the molecule;

5  $-\text{[(A)p]}-$  comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of:  $-\text{CH}_2-$ ,  $-\text{CHR}_3-$ ,  $-\text{CR}_4\text{R}_5-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}=\text{CR}_6-$ ,  $-\text{CR}_7-\text{CR}_8-$ ,  $-\text{C}=\text{C}-$ ,  $-\text{CR}_9=\text{CR}_{10}-$ ,  $-\text{C}\equiv\text{C}-$ , -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl  $-\text{(CO)}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NH}-$ ,  $-\text{HC}=\text{N}-$ ,  $-\text{CR}_{11}=\text{N}-$ , -

$\text{NR}_{12}-$ ,  $-\text{CS}-$ ,  $-\text{C}-$ ,  $-\text{C}-$ ,  $-\text{N}-$  and

p is an integer from 0 to 24;

10 each  $-\text{R}^4$  and  $-\text{R}_3$  through  $-\text{R}_5$  is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

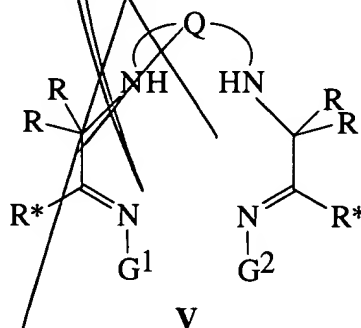
each  $-\text{R}^5$  and  $-\text{R}_6$  through  $-\text{R}_{12}$  is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted;

15 and all other groups are defined as in claim 35,

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom; and that at least one -R or  $-\text{R}^*$  group on the metal chelating radical  $-\text{K}_1$  of formulae **IIIa**, **IIIb**, or **IIIc** is  $-\text{[R}^3]-$ ;

or a pharmaceutically acceptable salt thereof.

52. A diagnostic or radiotherapeutic composition of claim 2 wherein  $\text{K}_1$ , or both  $\text{K}_1$  and  $\text{K}_5$  are metal chelating ligand radical of formula **V** that are chelated to radioactive metals



wherein

25  $-\text{Q}-$  is the group  $-(\text{C}(\text{RR}))_{m1}-(\text{Y}^1)_n-(\text{C}(\text{RR}))_{m2}-(\text{Y}^2-(\text{C}(\text{RR}))_{m3})_{n1}$ ;

$\text{Y}^1$  and  $\text{Y}^2$  are each independently  $-\text{CH}_2-$ ,  $-\text{NR}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{SO}-$ ,  $-\text{SO}_2-$  or  $-\text{Se}-$ ;

30 n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that  $m1 + m2 + n + n1$  is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and  $-\text{R}^*$  group is independently:  $-\text{R}^4$ ; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl,  $-\text{OR}^5$ ,  $-\text{C}(\text{O})-\text{R}^5$ ,  $-\text{C}(\text{O})-\text{N}(\text{R}^5)_2$ ,  $-\text{N}(\text{R}^5)_2$ ,  $-\text{N}(\text{R}^5)-\text{COR}^5$ , -alkyl- $\text{C}(\text{O})-\text{OR}^5$ , -alkyl- $\text{C}(\text{O})-\text{N}(\text{R}^5)_2$ , -alkyl- $\text{N}(\text{R}^5)_2$ , -alkyl- $\text{N}(\text{R}^5)-$



$\text{COR}^5$ ,  $-\text{aryl-C(O)-OR}^5$ ,  $-\text{aryl-C(O)-N(R}^5)_2$ ,  $-\text{aryl-N(R}^5)_2$ ,  $-\text{aryl-N(R}^5)\text{-COR}^5$ ,  $-\text{nitrile}$ ,  $-\text{acyl}$ ,  $-\text{acyloxy}$ ,  $-\text{heterocyclo}$ ,  $-\text{hydroxyalkyl}$ ,  $-\text{alkoxyalkyl}$ ,  $-\text{hydroxyaryl}$ ,  $-\text{arylalkyl}$ ,  $-\text{SO}_2\text{-R}^5$ ,  $-\text{alkyl-SO}_2\text{-R}^5$ , or  $-\text{[R}^3\text{]-}$ ;

wherein

$-\text{[R}^3\text{]-}$  is a linking group  $-\text{[(A)p]}_7$  that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae VIIa through VIId;

wherein  $-\text{[(A)p]}_7$  comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of:  $-\text{CH}_2-$ ,  $-\text{CHR}_3-$ ,  $-\text{CR}_4\text{R}_5-$ ,  $-\text{CH=CH}-$ ,  $-\text{CH=CR}_6-$ ,  $-\text{>CR}_7\text{-CR}_8<$ ,  $-\text{C=C}-$ ,  $-\text{CR}_9=\text{CR}_{10}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{cycloalkylidene}-$ ,  $-\text{cycloalkenyl}-$ ,  $-\text{arylidene}-$ ,  $-\text{heterocyclo}-$ , carbonyl  $(-\text{CO}-)$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,

$-\text{NH}-$ ,  $-\text{HC=N}-$ ,  $-\text{CR}_{11}=\text{N}-$ ,  $-\text{NR}_{12}-$ ,  $(-\text{CS}-)$ ,  $-\text{C}-$ ,  $-\text{C}^{\text{H}}-$ ,  $-\text{N}^{\text{H}}-$ , and

p is an integer from 0 to 24;

each  $-\text{R}^4$  and  $-\text{R}_3$  through  $-\text{R}_5$  is independently  $-\text{H}$ ,  $-\text{alkyl}$ ,  $-\text{alkoxy}$ ,  $-\text{hydroxy}$ ,  $-\text{cycloalkyl}$ ,  $-\text{hydroxyalkyl}$ ,  $-\text{aryl}$ , or  $-\text{heterocyclo}$ , each of which is optionally substituted;

each  $-\text{R}^5$  and  $\text{R}_6$  through  $\text{R}_{12}$  is independently  $-\text{H}$ ,  $-\text{alkyl}$ ,  $-\text{aryl}$ ,  $-\text{cycloalkyl}$  or  $-\text{hydroxyalkyl}$ , each of which is independently substituted; or

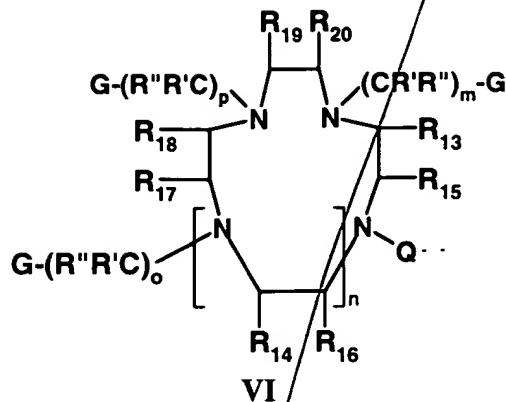
two R groups, or an R group and an  $\text{R}^*$  group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or  $\text{R}^*$  groups above;

each  $-\text{G}^1$  and  $-\text{G}^2$  is independently  $-\text{OH}$  or  $-(\text{NR}^6)_2$ ; with the proviso that at least one of  $-\text{G}^1$  or  $-\text{G}^2$  is  $-(\text{NR}^6)_2$ , and each  $-\text{R}^6$  is independently  $-\text{hydrogen}$ ,  $-\text{alkyl}$ ,  $-\text{aryl}$ ,  $-\text{acyl}$  or  $-\text{[R}^3\text{]-}$ ;

with the proviso that at least one  $-\text{R}$ ,  $-\text{R}^*$ , or  $-\text{R}^6$  group is  $-\text{[R}^3\text{]-}$ ;

or a pharmaceutically acceptable salt thereof.

53. The diagnostic composition of claim 46, wherein either  $\text{K}_1$ , or both  $\text{K}_1$  and  $\text{K}_5$  is a metal-chelating ligand radical of formula VI, that is chelated to a paramagnetic or superparamagnetic metal



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is  $-\text{C}(\text{R}')(\text{R}'')_{s1}-[\text{C}(\text{t})(\text{R}_{21})]_{s2}-[\text{C}(\text{R}_{22})(\text{R}_{23})]_{s3}-\text{X3}-\text{Y}-\text{X4}-$ ;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

Y is a single bond,  $-\text{C}(\text{R}_{25})(\text{R}_{26})-$ , or Y1 wherein,

Y1 is  $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$ , wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R27,  $-\text{C}(\text{O})\text{OR}_{28}$ ,  $-\text{P}(\text{O})(\text{OR}_{29})\text{OH}$ ,  $-\text{P}(\text{O})(\text{OR}_{30})\text{OR}_{31}$ ,

$-\text{P}(\text{O})(\text{OR}_{32})\text{R}_{33}$ ,  $-\text{P}(\text{O})(\text{OH})\text{R}_{34}$ ,  $-\text{C}(\text{O})\text{N}(\text{R}_{35})(\text{R}_{36})$ , or  $\text{C}(\text{O})\text{NH}(\text{R}_{37})$ ;

each G is independently  $-\text{C}(\text{O})\text{OR}'''$ ,  $-\text{P}(\text{O})(\text{OR}''')\text{OH}$ ,  $-\text{P}(\text{O})(\text{OR}''')_2$ ,

$-\text{P}(\text{O})(\text{OR}''')\text{R}''$ ,  $-\text{P}(\text{O})(\text{OH})\text{R}''$ ,  $\text{C}(\text{O})\text{N}(\text{R}''')_2$ , or  $\text{C}(\text{O})\text{NH}(\text{R}''')$ ;

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R13 through -R23, and -R25 through -R27 is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, aryl, or -heterocyclo, each of which is optionally substituted;

each -R24, and -R28 through -R37 is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R13 and R15 are each hydrogen and R17, together with R18, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R13,

together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen; or a pharmaceutically acceptable salt thereof.

5 54. A composition for radiographic imaging or radiotherapy in a kit form comprising  
a) a ligand of formula II in claim 2;  
b) a pharmaceutically acceptable reducing agent; and  
c) an optional buffering agent;  
in a lyophilized form.

10 55. A method for diagnostic imaging comprising the steps of:  
a) administering to a host the composition of claim 2 wherein K<sub>1</sub> is chelated to a radioactive, paramagnetic or superparamagnetic metal and K<sub>2</sub> is other than - K<sub>3</sub>; and  
b) obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic  
15 Resonance imaging techniques.

20 56. A method for diagnostic imaging comprising the steps of:  
a) administering to a host a composition of claim 2 wherein both K<sub>1</sub> and K<sub>5</sub> are chelated to a radioactive, paramagnetic or superparamagnetic metal; and  
b) obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic  
Resonance imaging techniques.

25 57. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim 2 wherein K<sub>1</sub> or both K<sub>1</sub> and K<sub>5</sub> are chelated to an alpha or beta emitting radioisotope.

30 58. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim 2 wherein K<sub>1</sub> is chelated to an alpha- or beta- emitting radioisotope and K<sub>2</sub> is other than - K<sub>3</sub>.

35 59. The diagnostic or radiotherapeutic composition of claim 1 wherein the folate receptor binding moiety is conjugated to the remainder of the molecule through the alpha carboxylate of its glutamate residue.

40 60. A composition for radiographic imaging or radiotherapy in a kit form comprising  
a) a folate receptor binding ligand of formula II in claim 2;  
b) a pharmaceutically acceptable reducing agent; and  
c) an optional buffering agent;  
in a lyophilized form.

45 61. The method of use for the diagnostic, therapeutic or radiotherapeutic composition of claim 2, comprising coinjection of:  
a) a folate-receptor binding ligand comprised of one or more folate-receptor binding residues conjugated to one or more macrocyclic or non-macrocyclic metal-chelating ligands which are chelated to a radioactive or non-radioactive metal

capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; and

- b) an unmetallated derivative of said folate-receptor binding ligand, administered at a dose level sufficient to affect the resulting biodistribution of the composition.

62. A method for neutron capture radiotherapy in a host in need thereof, comprising administering to said host the composition of claim 2 chelated to gadolinium, and after localization in the desired tissues, irradiating the tissues with neutrons to achieve emission of Auger electrons by the gadolinium to the extent that the desired tissue is damaged.

63. The diagnostic or radiodiagnostic method of claim 55 wherein said image is of tumors or tissues that overexpress folate binding protein.

64. The diagnostic or radiodiagnostic method of claim 55 wherein said image is of the kidneys of said host.

65. The diagnostic or radiodiagnostic method of claim 55 wherein said image is of the hepatobiliary system of said host.

66. The diagnostic or radiodiagnostic method of claim 56 wherein said image is of tumors or tissues that overexpress folate binding protein.

67. The diagnostic or radiodiagnostic method of claim 56 wherein said image is of the kidneys of said host.

68. The diagnostic or radiodiagnostic method of claim 56 wherein said image is of the hepatobiliary or gastrointestinal system of said host.

69. The diagnostic composition of formula **VIIa, VIIb, VIIc, or VIId** of claim 29, wherein  $W_1$  contains metal chelating ligands that are chelated to a paramagnetic or superparamagnetic metal.

70. The diagnostic composition of formula **VIIa, VIIb, VIIc, or VIId** of claim 29, wherein both  $W_1$  and  $W_2$  contains metal chelating ligands that are chelated to a paramagnetic or superparamagnetic metal.

71. The radiodiagnostic or radiotherapeutic composition of formula **VIIa – VIId** of claim 29 wherein  $W_1$  contains metal-chelating ligands that are chelated to a radioactive metal.

72. The radiodiagnostic or radiotherapeutic composition of formula **VIIa – VIId** of claim 29 wherein both  $W_1$  and  $W_2$  contain metal-chelating ligands that are chelated to a radioactive metal.

73. The diagnostic composition of formula **VIIa** - **VIIId** of claim **29** for visualization of tissues that overexpress folate binding protein using Nuclear Medicine imaging techniques, wherein either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal-chelating ligands chelated to a radioisotope of technetium, indium, copper, ruthenium, gallium or gadolinium.

74. The diagnostic composition of formula **VIIa** - **VIIId** of claim **29** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal-chelating ligands chelated to a paramagnetic or superparamagnetic metal.

75. The diagnostic composition of claim **74** wherein either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal-chelating ligands that are chelated to gadolinium.

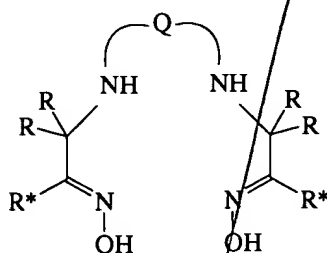
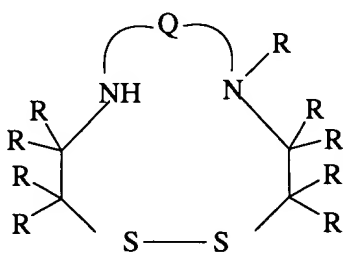
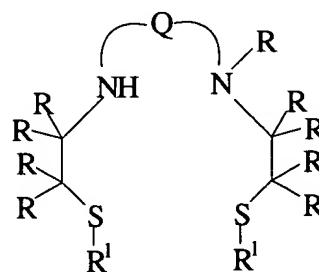
76. The diagnostic composition of claim **74** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein  $W_1$  contains metal chelating ligands that are chelated to paramagnetic or superparamagnetic metals.

77. The diagnostic composition of claim **74** for use in Magnetic Resonance imaging applications, wherein said paramagnetic metal is selected from the group consisting of: chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III).

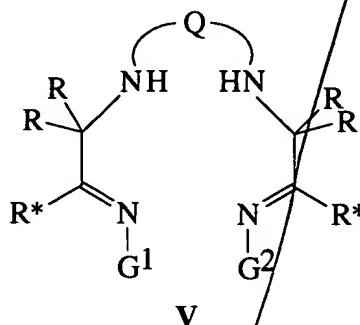
78. The diagnostic composition of claim **74** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein  $K_1$  is chelated to gadolinium.

79. The radiotherapeutic composition of claim **72** for radiotherapy of tissues that overexpress folate binding protein, wherein either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal-chelating ligands that are chelated to a radioisotope selected from the group consisting of  $^{153}\text{Samarium}$ ,  $^{156}\text{Holmium}$ ,  $^{165}\text{Dysprosium}$ ,  $^{203}\text{Lead}$ ,  $^{186}\text{Rhenium}$ ,  $^{188}\text{Rhenium}$ ,  $^{88}\text{Yttrium}$ ,  $^{90}\text{Yttrium}$ ,  $^{211}\text{Bismuth}$ ,  $^{212}\text{Bismuth}$ ,  $^{213}\text{Bismuth}$ , and  $^{214}\text{Bismuth}$ .

80. The radiodiagnostic or radiotherapeutic composition of claim **72** wherein either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain a metal-chelating ligand radical of formula **IIIa**, **IIIb**, or **IIIc**, that can chelate to a radioactive isotope,

**IIIa****IIIb****IIIc**

81. A diagnostic or radiotherapeutic composition of claim 29 wherein  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal chelating ligands of formula V that are chelated to a radioactive metal,



wherein

Q is the group  $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$ ;

$Y^1$  and  $Y^2$  are each independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

$n$  and  $n1$  are each independently 0 or 1; and  $m1$ ,  $m2$  and  $m3$  are independently 0 or an integer from 1 to 4; provided that  $m1$  and  $m2$  are not both 0, that  $m1 + m2 + n + n1$  is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each R and  $R^*$  group is independently:  $-H$ ,  $-R^4$ ;  $-alkoxy$ ;  $-hydroxy$ ;  $-halogen$ , especially fluoro,  $-haloalkyl$ ,  $-OR^5$ ,  $-C(O)-R^5$ ,  $-C(O)-N(R^5)_2$ ,  $-N(R^5)_2$ ,  $-N(R^5)-COR^5$ ,  $-alkyl-C(O)-OR^5$ ,  $-alkyl-C(O)-N(R^5)_2$ ,  $-alkyl-N(R^5)_2$ ,  $-alkyl-N(R^5)-COR^5$ ,  $-aryl-C(O)-OR^5$ ,  $-aryl-C(O)-N(R^5)_2$ ,  $-aryl-N(R^5)_2$ ,  $-aryl-N(R^5)-COR^5$ ,  $-nitrile$ ,  $-acyl$ ,  $-acyloxy$ ,  $-heterocyclo$ ,  $-hydroxyalkyl$ ,  $-alkoxyalkyl$ ,  $-hydroxyaryl$ ,  $-arylalkyl$ ,  $-SO_2-R^5$ ,  $-alkyl-SO_2-R^5$ , or  $-[R^3]-$ ;

wherein

each  $-[R^3]-$  is, in its entirety, the linking group  $-[(A)p^*]-$  that serves to couple the metal chelating ligand radical  $-K_5$  to  $-X-$ ;

each  $-R^4$  is independently  $-H$ ,  $-alkyl$ ,  $-alkoxy$ ,  $-hydroxy$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted;

each  $-R^5$  is independently  $-H$ ,  $-alkyl$ ,  $-aryl$ ,  $-cycloalkyl$  or  $-hydroxyalkyl$ , each of which is independently substituted;

or

two R groups, or an R group and an  $R^*$  group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or  $R^*$  groups above;

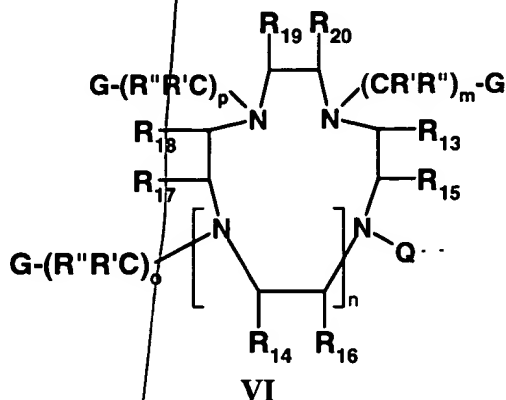
each  $-G^1$  and  $-G^2$  is independently  $-OH$  or  $-(NR^6)_2$ ; with the proviso that at least one of  $-G^1$  or  $-G^2$  is  $-(NR^6)_2$ , where each  $-R^6$  is independently  $-hydrogen$ ,  $-alkyl$ ,  $-aryl$ ,  $-acyl$  or  $-[R^3]-$ ; and

A is a linking group; and p is 0 or a positive integer;

with the proviso that at one to three  $-R$ ,  $-R^*$ , or  $-R^6$  groups is  $-[R^3]-$ ;

or a pharmaceutically acceptable salt thereof.

82. The diagnostic composition of claim 29, wherein either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal-chelating ligands of formula VI that are chelated to a paramagnetic or superparamagnetic metal,



wherein

$n$  is 0 or 1;

each  $m$ ,  $o$ , and  $p$  is independently 1 or 2;

$-Q-$  is  $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$ ;

wherein

$s1$ ,  $s2$ ,  $s3$ , and  $s4$  are independently 0 to 2;

$X3$ ,  $X4$ ,  $X5$ , and  $X6$  are independently a single bond,  $-O-$ ,  $-S-$ , or  $-N(R_{24})-$ ;

$Y$  is a single bond,  $-C(R_{25})(R_{26})-$ , or  $Y1$

wherein  $Y1$  is  $-C(=X5)-X6-W-$ ,

wherein  $W$  is a single bond,  $-alkylidene-$ ,  $-cycloalkylidene-$ ,  $-arylidene-$ ,  $-alkenylidene-$ , or  $-alkynylidene-$ , whose carbon atoms may or may not be substituted;

$t$  is  $-H$ ,  $-R_{27}$ ,  $-C(O)OR_{28}$ ,  $-P(O)(OR_{29})OH$ ,  $-$

$P(O)(OR_{30})OR_{31}$ ,  $-P(O)(OR_{32})R_{33}$ ,  $-P(O)(OH)R_{34}$ ,  $-C(O)N(R_{35})(R_{36})$ , or  $C(O)NH(R_{37})$ ;

each  $G$  is independently  $-C(O)OR'''$ ,  $-P(O)(OR''')OH$ ,  $-P(O)(OR''')_2$ ,  $-P(O)(OR'')R'''$ ,  $-P(O)(OH)R''$

$C(O)N(R''')_2$ , or  $C(O)NH(R''')$ ;

each  $-R'$  and  $-R''$  is independently a single bond,  $-H$ ,  $-alkyl$ ,  $-alkoxy$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted,

each  $-R'''$  is independently a  $-H$ ,  $-alkyl$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted,

each  $-R_{13}$  through  $-R_{23}$ , and  $R_{25}$  through  $-R_{27}$  is independently  $-H$ ,  $-alkyl$ ,  $-alkoxy$ ,  $-halogen$ ,  $-hydroxy$ ,  $-cycloalkyl$ ,  $-hydroxyalkyl$ ,  $-aryl$ , or  $-heterocyclo$ , each of which is optionally substituted;

each -R<sub>24</sub>, and -R<sub>28</sub> through -R<sub>37</sub> is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R<sub>13</sub> together with R<sub>15</sub>, and R<sub>17</sub> together with R<sub>18</sub>, independently form, together with the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R<sub>13</sub> and R<sub>15</sub> are each hydrogen and R<sub>17</sub>, together with R<sub>18</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R<sub>13</sub>, together with R<sub>15</sub>, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R<sub>17</sub> and R<sub>18</sub> are hydrogen;

or a pharmaceutically acceptable salt thereof.

83. A composition for radiographic imaging or radiotherapy in a kit form comprising  
 a) a ligand of formula VIIa-VIIId in claim 29;  
 b) a pharmaceutically acceptable reducing agent; and  
 c) an optional buffering agent;  
 in a lyophilized form.

84. A method for diagnostic imaging comprising the steps of: administering to a host the composition of claim 29 wherein W<sub>1</sub> contains a metal chelate that is chelated to a radioactive, paramagnetic or superparamagnetic metal; and obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic Resonance imaging techniques.

85. A method for diagnostic imaging comprising the steps of: administering to a host a composition of claim 29 wherein both W<sub>1</sub> and W<sub>2</sub> contains a metal chelate that is chelated to a radioactive, paramagnetic or superparamagnetic metal; and obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic Resonance imaging techniques.

86. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim 29 wherein W<sub>1</sub> or both W<sub>1</sub> and W<sub>2</sub> contain macrocyclic ligands that are chelated to an alpha or beta emitting radioisotope.

87. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim 29 wherein W<sub>1</sub> contains macrocyclic ligands that are chelated to an alpha or beta emitting radioisotope.

88. The diagnostic or radiotherapeutic composition of claim 29 wherein the folate receptor binding moiety is conjugated to the remainder of the molecule through the alpha carboxylate of its glutamate residue.

89. The method of use for the diagnostic, therapeutic or radiotherapeutic composition of claim 29, comprising coinjection of:



- 5 a) a folate-receptor binding ligand comprised of one or more folate-receptor binding residues conjugated to one or more macrocyclic or non-macrocyclic metal-chelating ligands which are chelated to a radioactive or non-radioactive metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; and
- b) an unmetallated derivative of said folate-receptor binding ligand, administered at a dose level sufficient to affect the resulting biodistribution of the composition.

10 90. A method for neutron capture radiotherapy in a host in need thereof, comprising administering to said host the composition of formula **VIIa-VIIId** of claim **29** wherein the metal chelating ligands in  $W_1$ ,  $W_2$  or  $W_1$  and  $W_2$  are chelated to gadolinium, and after localization of said compound in the desired tissues, irradiating the tissues with neutrons to achieve emission of Auger electrons by the gadolinium to the extent that the desired tissue

15 is damaged.

91. The diagnostic or radiodiagnostic method of claim **84** wherein said image is of tumors or tissues that overexpress folate binding protein.

20 92. The diagnostic or radiodiagnostic method of claim **84** wherein said image is of the kidneys of said host.

93. The diagnostic or radiodiagnostic method of claim **84** wherein said image is of the hepatobiliary system of said host.

25 94. The diagnostic or radiodiagnostic method of claim **85** wherein said image is of tumors or tissues that overexpress folate binding protein.

95. The diagnostic or radiodiagnostic method of claim **85** wherein said image is of the kidneys of said host.

30

96. The diagnostic or radiodiagnostic method of claim **85** wherein said image is of the hepatobiliary system of said host.

35 97. A method for diagnostic imaging comprising the steps of: administering to a host the diagnostic composition of claim **29** comprising dendrimeric conjugates of formulae **VIIa, VIIb, VIIc, or VIId**, wherein  $W_1$  contains metal chelating ligands that are chelated to a radioactive gamma-emitting metal, and obtaining a radiodiagnostic image of said host.

40 98. The diagnostic composition of formulae **IXa, IXb, IXc, or IXd** of claim **36** containing metal chelating ligands that are chelated to a paramagnetic or superparamagnetic metal.

99. The diagnostic composition of formula **IXa, IXb, IXc, or IXd** of claim **98** wherein

45 the folate receptor binding residues are chelated to the remainder of the molecule only

through the alpha carboxylate residue.

100. The diagnostic composition of formula **IXa**, **IXb**, **IXc**, or **IXd** of claim **36** for visualization of tissues that overexpress folate binding protein using Nuclear Medicine imaging techniques, wherein said compounds contain macrocyclic metal-chelating ligands chelated to a radioisotope of technetium, indium, copper, ruthenium, gallium or gadolinium.

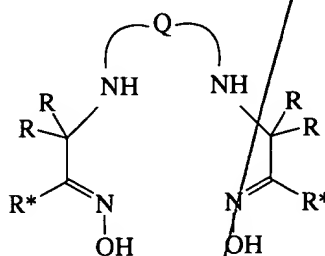
101. The diagnostic composition of formula **IXa**, **IXb**, **IXc**, or **IXd** of claim **36** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein the folate-receptor binding residue is conjugated to the remainder of the molecule via its alpha carboxylate moiety, and the compound contains macrocyclic metal-chelating ligands chelated to a paramagnetic or superparamagnetic metal.

102. The diagnostic composition of claim **101** for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging wherein, either  $W_1$ ,  $W_2$  or both  $W_1$  and  $W_2$  contain metal-chelating ligands that are chelated to gadolinium.

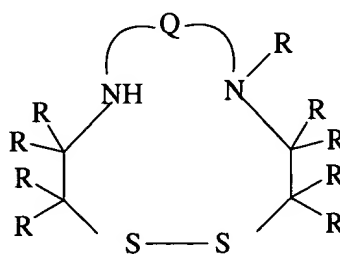
103. The diagnostic composition of claim **101** for use in Magnetic Resonance imaging applications, wherein said paramagnetic metal is selected from the group consisting of: chromium (III), manganese (II), iron (II), iron (III), cobalt (II), nickel (II), copper (II), praseodymium (III), neodymium (III), samarium (III), gadolinium (III), terbium (III), dysprosium (III), holmium (III), erbium (III) and ytterbium (III).

104. The radiotherapeutic composition of claim **36** for radiotherapy of tissues that overexpress folate binding protein, containing metal-chelating ligands that are chelated to a radioisotope selected from the group consisting of  $^{153}\text{Samarium}$ ,  $^{156}\text{Holmium}$ ,  $^{165}\text{Dysprosium}$ ,  $^{203}\text{Lead}$ ,  $^{186}\text{Rhenium}$ ,  $^{188}\text{Rhenium}$ ,  $^{88}\text{Yttrium}$ ,  $^{90}\text{Yttrium}$ ,  $^{211}\text{Bismuth}$ ,  $^{212}\text{Bismuth}$ ,  $^{213}\text{Bismuth}$ , and  $^{214}\text{Bismuth}$ .

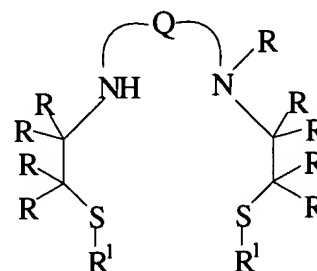
105. The radiodiagnostic or radiotherapeutic composition of claim **36**, wherein the metal-chelating ligand is a radical of formula **IIIa**, **IIIb**, or **IIIc**.



**IIIa**

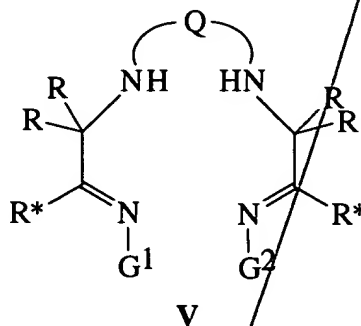


**IIIb**



**IIIc**

106. The radiodiagnostic or radiotherapeutic composition of claim **36** wherein the metal-chelating ligand is a radical of formula **V** that is chelated to a radioactive metal,



wherein

-Q- is the group  $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$ ;

$Y^1$  and  $Y^2$  are each independently  $-CH_2-$ ,  $-NR-$ ,  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$  or  $-Se-$ ;

n and  $n1$  are each independently 0 or 1; and  $m1$ ,  $m2$  and  $m3$  are independently 0 or an integer from 1 to 4; provided that  $m1$  and  $m2$  are not both 0, that  $m1 + m2 + n + n1$  is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each -R and -R\* group is independently:  $-R^4$ ; -alkoxy; -hydroxy; -halogen, especially fluoro, -haloalkyl,  $-OR^5$ ,  $-C(O)-R^5$ ,  $-C(O)-N(R^5)_2$ ,  $-N(R^5)_2$ ,  $-N(R^5)-COR^5$ , -alkyl- $C(O)-OR^5$ , -alkyl- $C(O)-N(R^5)_2$ , -alkyl- $N(R^5)_2$ , -alkyl- $N(R^5)-COR^5$ , -aryl- $C(O)-OR^5$ , -aryl- $C(O)-N(R^5)_2$ , aryl- $N(R^5)_2$ , -aryl- $N(R^5)-COR^5$ , -nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl, arylalkyl,  $-SO_2-R^5$ , -alkyl- $SO_2-R^5$ , or  $-[R^3]-$ ;

wherein

$-[R^3]-$  is a linking group  $-[(A)p]-$  that links the metal chelating ligand radical of formula V to the remainder of the molecule of formulae VIIa through VIId;

wherein  $-[(A)p]-$  comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of:  $-CH_2-$ ,  $-CHR_3-$ ,  $-CR_4R_5-$ ,  $-CH=CH-$ ,  $-CH=CR_6-$ ,  $>CR_7-CR_8<$ ,  $-C=C-$ ,  $-CR_9=CR_{10}-$ ,  $-C\equiv C-$ , -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ( $-CO-$ ),  $-O-$ ,  $-S-$ ,

$-NH-$ ,  $-HC=N-$ ,  $-CR_{11}=N-$ ,  $-NR_{12}-$ ,  $(-CS-)$ ,  $-\overset{H}{\underset{|}{C}}-$ ,  $-\overset{H}{\underset{|}{C}}-$ ,  $-\overset{H}{\underset{|}{N}}-$ , and

p is an integer from 0 to 24;

each  $-R^4$  and  $-R_3$  through  $-R_5$  is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each  $-R^5$  and  $R_6$  through  $R_{12}$  is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

two R groups, or an R group and an R\* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated,

spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R\* groups above;

each -G<sup>1</sup> and -G<sup>2</sup> is independently -OH or -(NR<sup>6</sup>)<sub>2</sub>; with the proviso that at

least one of -G<sup>1</sup> or -G<sup>2</sup> is -(NR<sup>6</sup>)<sub>2</sub>, and each -R<sup>6</sup> is independently -

hydrogen, -alkyl, -aryl, -acyl or -[R<sup>3</sup>]-;

with the proviso that at least one -R, -R\*, or -R<sup>6</sup> group is -[R<sup>3</sup>]-;

or a pharmaceutically acceptable salt thereof.

107. The diagnostic composition of claim 36 wherein the metal-chelating ligand is a radical of formula VI that is chelated to a paramagnetic or superparamagnetic metal.

108. A composition for radiographic imaging or radiotherapy in a kit form comprising

a) a ligand of formula IXa - IXd in claim 36;

b) a pharmaceutically acceptable reducing agent; and

c) an optional buffering agent;

in a lyophilized form.

109. A method for diagnostic imaging comprising the steps of: administering to a host the composition of claim 108 wherein said ligand of formula IXa - IXd is chelated to a radioactive, paramagnetic or superparamagnetic metal; and obtaining a diagnostic image of said host using Nuclear Medicine or Magnetic Resonance imaging techniques.

110. A method for radiotherapy comprising the steps of: administering to a host the composition of formula IXa - IXd of claim 36 containing macrocyclic metal chelating ligands that are chelated to an alpha or beta emitting radioisotope, in sufficient amount to bring about a beneficial effect.

111. A method for radiotherapy comprising the steps of: administering to a host in need thereof the composition of claim 36 wherein W<sub>1</sub> contains macrocyclic ligands that are chelated to an alpha or beta emitting radioisotope.

112. The use of diagnostic or radiotherapeutic composition of claim 36 for magnetic resonance imaging, wherein the folate receptor binding moieties in said compound are conjugated to the remainder of the molecule through the alpha carboxylate of its glutamate residue.

113. The method of use for the diagnostic, therapeutic or radiotherapeutic composition of claim 36 comprising: coinjection of:

a) a folate-receptor binding ligand comprised of one or more folate-receptor binding residues conjugated to one or more macrocyclic or non-macrocyclic metal-chelating ligands which are chelated to a radioactive or non-radioactive metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a therapeutic or radiotherapeutic effect; and

b) an unmetallated derivative of said folate-receptor binding ligand,

administered at a dose level sufficient to affect the resulting biodistribution of the composition.

114. A method for neutron capture radiotherapy in a host in need thereof, comprising administering to said host the composition of formulae **IXa-IXd** of claim **36** wherein the metal chelating ligands are chelated to gadolinium, and after localization of said compound in the desired tissues, irradiating the tissues with neutrons to achieve emission of Auger electrons by the gadolinium to the extent that the desired tissue is damaged.

115. The diagnostic or radiodiagnostic method of claim **109** wherein said image is of tumors or tissues that overexpress folate binding protein.

116. The diagnostic or radiodiagnostic method of claim **109** wherein said image is of the kidneys of said host.

117. The diagnostic or radiodiagnostic method of claim **109** wherein said image is of the hepatobiliary system of said host.

118. The composition of claim **1** for chemotherapy comprising: a derivative of folic acid coupled to a cancer therapy drug through the alpha carboxylate of folic acid, or coupled through both the alpha and gamma carboxylates of folic acid, in a pharmaceutically acceptable carrier.

119. A composition for therapy or radiotherapy of tissues or organs that overexpress folate-binding protein comprising a folate-receptor binding derivative of folic acid comprising one or more folic acid derivatives, at least one of which is conjugated through its alpha carboxylate via an optional linking group to a chemotherapeutic drug, in a pharmaceutically acceptable carrier.

120. A composition of claim **1** for chemotherapy comprising:  
a) a metal chelating ligand;  
b) a radioactive metal chelated by said ligand;  
c) a chemotherapy drug coupled to said ligand said complex coupled to  
d) a derivative of folic acid through its alpha carboxylate or through both the alpha and gamma carboxylate of folic acid, in  
e) a pharmaceutically acceptable carrier.

121. A composition of claim **1** for radiographic imaging or radiotherapy in a kit form comprising

- a) a folate receptor-binding analog of folate coupled through either the alpha carboxylate of folic acid or through both the alpha and gamma carboxylates of folic acid to;
- b) a metal chelating ligand for complexation with a radioisotope;
- c) a pharmaceutically acceptable reducing agent; and
- d) a buffering agent;

in a lyophilized form.

122. The diagnostic composition of claim 18 for visualization of tissues that overexpress folate binding protein using magnetic resonance imaging, wherein  $K_5$  is chelated to gadolinium.

123. A method for diagnostic imaging comprising the steps of: administering to a host the composition of claim 18 wherein said ligand is chelated to gadolinium; and obtaining a diagnostic image using Magnetic Resonance imaging techniques.

124. An intermediates useful for the preparation of the compounds of claim 1 selected from the group consisting of:

Methyl 3-azido-2-hydroxypropionate;

Methyl 3-azido-2-trifluoromethanesulfonyloxypropionate;

Tris-t-butyl N-12-(3-azido-2-methoxycarbonyl-1-ethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate;

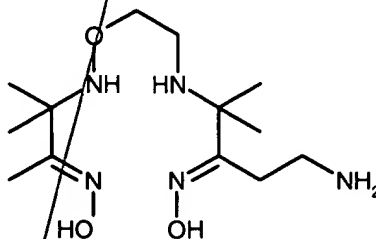
Tris-t-butyl N-12-(3-amino-2-methoxycarbonyl-1-ethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-tricarboxylate;

3-Amino-[1,5-bis(benzyloxycarbonyl)-3-[2-(benzyloxycarbonyl)ethyl]pentane;

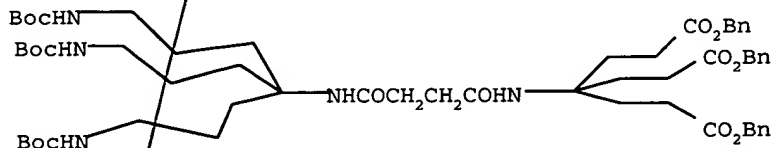
and

N-[1,5-Bis(benzyloxycarbonyl)-3-[2-(benzyloxycarbonyl)ethyl]-3-pentyl]-butanedioic monoamide.

125. The intermediate 12-Amino-3,3,9,9-tetramethyl-5-oxa-4,8-diaza-2,10-dodecane-dione dioxime, useful for the preparation of compounds of claim 1 having the structure:



126. The intermediate N-[1,5-Bis(benzyloxycarbonyl)-3-[2-(benzyloxycarbonyl)-ethyl]-3-pentyl]-N'-[1,7-bis-(t-butoxycarbonyl)amino-[4-(3-(t-butyloxycarbonyl)propyl)-4-heptyl]butanedioic diamide, useful for the preparation of compounds of claim 35 having the structure:



127. The intermediate Tris-t-butyl N-12-(3-amino-2-methoxycarbonyl-1-ethyl)-1,4,7,10-

tetracyclododecane-1,4,7-tricarboxylate useful for the preparation of compounds of claim 28, having the structure:

